REMARKS

Claims 87-116 are pending in this application. In view of its withdrawal from consideration, claim 89 has been canceled without prejudice to Applicants' right to pursue the subject matter of the canceled claim in a related application. Claims 117 and 118 have been added to more particularly point out what Applicants regard as the invention. In order to expedite the prosecution of the application and without conceding to the validity of the Examiner's rejections, claims 87, 88, 90, 91, 102, 107 and 108 have been amended to more particularly point out what Applicants regard as the invention. In particular, claims 87, 88, 90, and 91 have been amended to insert the phrase "numbered according to the EU index as in Kabat," and claims 87 and 91 have been amended to specify that at least one of the amino acid substitutions is at amino acid residue 252, 254, 256, 309, 311, 433 or 434. Claims 87, 88, 90, 91, and 102 have been amended to recite substitution with "glutamic acid" and "aspartic acid" at position 256, and "histidine, phenylalanine, or tyrosine" at position 434, as appropriate. Applicants note that the previous claim terms "glutamate" and "aspartate" are equivalent terms for "glutamic acid" and "aspartic acid." In addition, "lysine" has been deleted from the group of possible amino acid substitutions at position 433 in claims 87, 90 and 91. Further, "alanine" and "asparagine" have been deleted from the group of possible amino acid substitutions at position 256 in claims 87 and 102. Support for the amendments to claims 87, 88, 90, 91 and 102 is found in the specification, *inter alia,* at page 4, lines 32-35; at page 6, lines 25-26; and at page 7, lines 6-7. The amendments are fully supported by the specification of the present application and do not constitute new matter. Upon entry of this Amendment, claims 87, 88, and 90-118 will be pending and under examination.

Applicants thank the Examiner for granting an interview with Applicants' attorneys on February 23, 2005. The Examiner's comments were taken into consideration in drafting this response. The substance of the interview is discussed throughout the Amendment. The amendments and remarks made herein are designed to place the application into condition for allowance. As such, Applicants respectfully request that the amendments and remarks made herein be entered into the record of the application and fully considered by the Examiner.

1. FORMALITIES

The Examiner has withdrawn claim 89 as allegedly directed to a nonelected invention. In response, Applicants have canceled claim 89.

2. THE REJECTIONS UNDER 35 U.S.C. §112, SECOND PARAGRAPH, SHOULD BE WITHDRAWN

Claims 87, 88 and 90-116 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner contends that the recitation of amino acid positions in the claims without providing a sequence identification number is indefinite and ambiguous. In the February 23, 2005 interview, the Examiner stated that it was the policy of the Patent Office to require a sequence identifier in any claim referring to particular amino acid residues. The Examiner maintained his view that strict adherence to this policy was required, notwithstanding the Examiner's acknowledgment that immunoglobulins represent a special case where the art has developed a uniform common numbering scheme that is applicable to all immunoglobulin proteins, i.e., the Kabat numbering system. Applicants respectfully maintain that the reference in the claims to particular amino acid residues of an IgG constant domain *numbered according to the EU index as in Kabat* is clear and definite for the reasons of record and for the additional reasons set forth in greater detail below.

The independent claims 87, 88, and 90 recite, in relevant part, a modified IgG comprising a human IgG constant domain comprising one or more amino acid substitutions relative to a wild-type human IgG constant domain at one of more amino acid residues at specified amino acid positions, *numbered according to the EU index as in Kabat.* Independent claim 91 recites, in relevant part, a modified IgG comprising a non-human IgG constant domain comprising one or more amino acid substitutions relative to a wild-type non-human IgG constant domain at one or more amino acid residues at specified amino acid positions, *numbered according to the EU index as in Kabat.*

As indicated in the specification at page 4, lines 32-35, all residues of the IgG constant domain are numbered according to the Kabat numbering system and as presented in Figure 2 (SEQ ID NO: 83). The Kabat numbering system is described in Kabat et al. 1991,

Sequences of Proteins of Immunological Interest, Fifth Edition, NIH Publication No. 91-3242 (hereinafter, "Kabat"). The Kabat system was known in the art at the time of filing this application, as demonstrated by Johnson and Wu, 2000, attached hereto as **Exhibit A**, which refers to the "now-known Kabat numbering system" in the Abstract at page 214.

Importantly, the Kabat numbering system is not based on any one particular sequence. Instead, it is based on a global sequence alignment derived from the alignment of many individual immunoglobulin sequences (see, e.g., the selected pages from Kabat attached hereto as **Exhibit B**). The result is a numbering system that is applicable to all immunoglobulin sequences. Applicants maintain that any given immunoglobulin sequence can be numbered according to Kabat using methods of ordinary skill in the art at the time of filing, for example, using the sequences and tools provided by the Kabat database (see e.g., Johnson and Wu, p. 214, col. 2). In order to exemplify this numbering system and underscore how it is used to reference particular amino acid residues in a sequence, Applicants refer the Examiner to pages 679-87 of Kabat, attached in Exhibit B, which depict the Kabat numbering for the human IgG1 heavy chain constant region CH2. The table lists the constant domain amino acid positions 243-359 according to the Kabat, the EU index, and the OU index in the first three columns. The fourth column gives the identity and location of the amino acid residues that were invariant over the aligned sequences. The next 159 columns give the amino acid residue at each of amino acid positions 243-359 for 159 aligned sequences. Finally, the final four columns provide certain statistics for the alignment at each position. It is clear from this table that each position numbered according to Kabat refers to a definite amino acid in the alignment. Applicants maintain that the identity of the particular amino acid at any position can be determined for any aligned immunoglobulin sequence using methods that were publicly available and within the routine skill in the art at the time of filing this application.

In summary, Applicants maintain that each position in a sequence numbered according to Kabat has a clear and definite meaning to one of skill in the art. Therefore, the recitation of particular amino acid residue positions, numbered according to the EU index as in Kabat, in claims 87-91 is clear and definite without reference to a particular sequence. In response to the Examiner's statements regarding Patent Office policy, Applicants point out that the Office has recently issued a number of patents with claims which reference particular amino acid positions in immunoglobulin sequences according to Kabat without providing a

sequence identifier (see e.g., U.S. Patent Nos. 6,528,624, 6,538,124 and 6,737,056 made of record in Applicants' Supplemental Information Disclosure Statement filed herewith). Accordingly, Applicants respectfully assert that claims 87, 88 and 90-116 satisfy the requirements of 35 U.S.C. §112, second paragraph, and respectfully request that the Examiner's rejection be withdrawn.

The Examiner also rejected claim 107 as allegedly indefinite and ambiguous for reciting "the heavy and light chain variable domain of palivizumab" without reciting a sequence identifier. The Examiner stated in the February 23, 2005 interview that amending the claim to recite the appropriate sequence identifiers would overcome this rejection.

In response, Applicants maintain that the claim is clear and definite because the sequence of the heavy and light chain variable domain of palivizumab was known in the art at the time the subject application was filed. For example, the sequence is described in Johnson et al., J. Infectious Disease 176:1215-24, 1997, which is incorporated by reference in the specification at page 8, lines 5-6, and which was made of record in the Information Disclosure Statement previously filed in connection with this application. However, in order to expedite the prosecution of this application, and in accordance with the Examiner's recommendation, Applicants have amended claim 107 to recite the appropriate sequence identifiers. Support for this amendment is found in the specification at Table III on page 27 which provides the VH and VL domain sequence identifiers for SYNAGIS®. Applicants maintain that SYNAGIS® was known in the art as the commerical name for palivizumab (see e.g., remarks below and the 2001 Physician's Desk Reference entry for SYNAGIS® enclosed as **Exhibit D**).

3. THE REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN

Claim 107 is rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention. Specifically, the Examiner has required that Applicants demonstrate that SYNAGIS® is and was commercially available at the time the application was filed. The Examiner noted that Applicants' Exhibit A, which purported to demonstrate this, was not enclosed with Applicants' Amendment filed September 7, 2004. The Examiner stated in the February 23,

2005 interview that a copy of the appropriate pages showing the entry for SYNAGIS® from the Physicians' Desk Reference would overcome this rejection.

In response, Applicants note that their return receipt postcard bearing the date stamp of September 7, 2004 from the Patent Office lists as item No. 7: "Exhibit A, SYNAGIS® product information from the 2001 and 2004 Physicians' Desk Reference." A copy of the postcard is attached hereto as **Exhibit C**. Accordingly, Applicants maintain that Exhibit A was enclosed with their September 7, 2004 Amendment. However, in order to expedite the prosecution of this application, Applicants enclose herewith as **Exhibit D** a copy of the Exhibit A that was enclosed with their September 7, 2004 response. Applicants maintain that Exhibit D demonstrates that palivizumab is the generic name of SYNAGIS® and that SYNAGIS® was known and commercially available as of the effective filing date of the subject application. Accordingly, Applicants maintain that claim 107 satisfies the requirements of 35 U.S.C. §112, first paragraph, and respectfully request that the Examiner withdraw this rejection.

4. THE REJECTIONS UNDER 35 U.S.C. §102 SHOULD BE WITHDRAWN

Claims 87, 92, 93, 95, 96, and 108-116 are rejected under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent No. 6,277,375 ("the Ward patent"). Specifically, the Examiner contends that the Ward patent does teach "amino acid substitution with threonine at amino acid residues 252, 254, or 256 of an IgG," and therefore, anticipates the claimed invention. In the February 23, 2005 interview, the Examiner conceded that Applicants' argument, set forth below, was persuasive and that the rejections under 35 U.S.C. §102(e) should be withdrawn.

In order to anticipate the claimed invention, a single reference must teach each and every element of the claims. Verdegaal Bros. v. Union Oil Co., 814 F.2d 628 (Fed. Cir. 1987). Applicants maintain that the Ward patent does not teach each and every element of claim 87. Specifically, the Ward patent does not teach the particular amino acid substitutions at positions 252, 254, and 256 that are recited in claim 87. For example, the Ward patent does not teach a substitution at position 252 with tyrosine, phenylalanine, tryptophan or threonine. Nor does the Ward patent teach a substitution at position 254 with threonine or a substitution at position 256 with serine, arginine, glutamine, glutamate, asparate, alanine, asparagine or threonine.

Importantly, while the Ward patent teaches threonine at positions 252, 254, and 256, the Ward patent does not teach a *substitution* of some other residue at position 252, 254, or 256 *with threonine* (see col. 3, lines 39-46). Instead, the Ward patent teaches only the substitution *of threonine* at position 252, 254, or 256 *with other residues*, none of which are the residues recited in claim 87 of the subject application. Specifically, the Ward patent teaches substitution *of threonine* at 252 *with leucine*; substitution *of threonine* at 254 *with serine*; and substitution *of threonine* 256 *with phenylalanine* (see col. 3, lines 56-64).

In view of the fact that the Ward patent does not teach the specific amino acid substitutions at positions 252, 254, and 256 recited by claim 87, Applicants maintain that the Examiner's rejection of claim 87 as anticipated by Ward is improper and respectfully request that the rejection be withdrawn. Likewise, Applicants respectfully request the withdrawal of the rejection of claims 92, 93, 95, 96, and 108-116 under 35 U.S.C. § 102(e), each of which depends from claim 87.

5. THE REJECTIONS UNDER 35 U.S.C. §103 SHOULD BE WITHDRAWN

Claims 106 and 107 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent No. 6,277,375 ("the Ward patent") in view of U.S. Patent No. 6,572,856 ("the Taylor patent"). Specifically, the Examiner contends that it would have been obvious for one of skill in the art to combine the teachings of the Ward patent with the teachings of the Taylor patent in order to arrive at the invention of claims 106 and 107. In the February 23, 2005 interview, the Examiner conceded that Applicants' argument, set forth below, was persuasive and that the rejections under 35 U.S.C. §103 should be withdrawn.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate three things with respect to each claim. In re Vaeck, 947 F.2d 488 (Fed. Cir. 1991). First, that the cited references, when combined, teach or suggest every element of the claim. Second, that one of ordinary skill would have been motivated to combine the teachings of the cited references at the time of the invention. Third, that there would have been a reasonable expectation that the claimed invention would succeed.

Applicants maintain that the cited references fail to support a *prima facie* case of obviousness because the Taylor patent does not overcome the deficiency of the Ward patent in failing to teach the specific amino acid substitutions at positions 252, 254, and 256 recited

in claim 87, from which claims 106 and 107 depend. Thus, the cited references combined fail to teach each and every element of the claims. Given this failure, Applicants also maintain that in view of such references, neither a motive to combine nor a reasonable expectation of success can exist. Accordingly, Applicants maintain that claims 106 and 107 are not *prima facie* obvious over the Ward patent in view of the Taylor patent and respectfully request that the Examiner withdraw this rejection.

6. THE REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN

Claims 87, 91, 93, 94, and 95-116 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner contends that the claims lack support in the specification as originally filed for the following:

(i) In claims 87, 91, and 102: substitution at amino acid residue
252 with threonine;
256 with aspartate, alanine, or asparagine;
433 with isoleucine, proline, or glutamine; and
434 with histidine, asparagine, arginine, threonine, lysine or methionine;

(ii) In claims 93, 94, and 103: substitution at amino acid residue
385 with threonine, histidine, lysine, alanine or glycine;
386 with aspartic acid, serine, lysine, arginine, isoleucine, or methionine; and
387 with proline, histidine, serine, threonine, or alanine;

(iii) a modified IgG as recited in claims 96, 98, and 99-101; and
(iv) a modified IgG which has the heavy and light chain of palivizumab as recited in claim 107.

In the February 23, 2005 interview, Applicants advised the Examiner that they would provide support from the specification for the amino acid substitutions recited in the claims. Accordingly, Applicants respectfully traverse the Examiner's rejection and maintain that the claims are fully supported by the specification as originally filed. Applicants note that claims 87, 91, and 102 have been amended to recite substitution with "apartic acid" at amino acid position 256 and "histidine, phenylalanine, or tyrosine" at amino acid position 434. Further, Applicants note that claims 87 and 102 have been amended to delete substitution with alanine or asparagine at amino acid position 256.

Applicants point to the following support in the specification for the amino acid substitutions recited in claims 87, 91, 102, 93, 94, and 103:

Substitution at:	With:	Specification
252	threonine:	p. 6, *ll.* 23-24; p. 15, *ll.* 33-34
256	aspartic acid, alanine, or asparagine:	p. 6, *ll.* 25-27; p. 15, *l.* 36 to p. 16, *l.* 1
433	isoleucine, proline, or glutamine:	p. 7, *ll.* 5-6; p. 16, *ll.* 8-9
434	histidine, phenylalanine, or tyrosine:	p. 7, *ll.* 6-7; p. 16, *l.* 10
385	threonine, histidine, lysine, alanine, or glycine:	p. 7, *ll.* 16-17; Table I, p. 19; p. 16 *ll.* 16-17
386	aspartic acid, serine, lysine, arginine, isoleucine, or methionine:	p. 7, *ll.* 17-19; p. 16, *ll.* 17-19
387	proline, histidine, serine, threonine, or alanine:	p. 7, *ll.* 19-20; p. 16, *ll.* 19-20

Support for the recitation of the particular IgG isotype IgG_1, IgG_2, IgG_3 and IgG_4 in claims 96, 99, 100, and 101 is found in the specification at page 20, lines 5-6. Support for the recitation of the particular IgG isotypes IgG_1, IgG_{2a}, IgG_{2b}, IgG_{2c} and IgG_3 in claim 98 is found in the specification at page 20, line 7.

Finally, in response to the Examiner's rejection of claim 107 for recitation of the term "palivizumab", Applicants point out that "palivizumab" is a generic term for SYNAGIS®, which is described in the specification at page 8, lines 2-5. Applicants maintain that it is proper to use the generic term instead of the trademark name in the claim since the trademark is used to identify a source of goods, not the goods themselves. In fact, the use of a trademark name as a limitation of a claim is improper according to M.P.E.P. §2173.05(u). Since "palivizumab" was known in the art as the generic term for SYNAGIS®, as indicated at page 1863 of the 2001 Physicians Desk Reference attached hereto as Exhibit D, Applicants maintain that it is proper to use the term "palivizumab" in claim 107.

Accordingly, Applicants maintain that claims 87, 91, 93, 94, and 95-116 satisfy the requirements of 35 U.S.C. §112, first paragraph, and respectfully request that this rejection be withdrawn.

CONCLUSION

Applicants believe that the present claims meet all of the requirements for patentability. Entry and consideration of the foregoing amendments and remarks into the file of the subject application is respectfully requested.

If a telephone interview would be of assistance in advancing prosecution of the subject application, Applicants' undersigned attorney invites the Examiner to telephone her at the number provided below.

Respectfully submitted,

Date: April 18, 2005

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Kabat Database and its applications: 30 years after the first variability plot

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ABSTRACT

The Kabat Database was initially started in 1970 to determine the combining site of antibodies based on the available amino acid sequences at that time. Bence Jones proteins, mostly from human, were aligned, using the now-known Kabat numbering system, and a quantitative measure, variability, was calculated for every position. Three peaks, at positions 24–34, 50–56 and 89–97, were identified and proposed to form the complementarity determining regions (CDR) of light chains. Subsequently, antibody heavy chain amino acid sequences were also aligned using a different numbering system, since the locations of their CDRs (31–35B, 50–65 and 95–102) are different from those of the light chains. CDRL1 starts right after the first invariant Cys 23 of light chains, while CDRH1 is eight amino acid residues away from the first invariant Cys 22 of heavy chains. During the past 30 years, the Kabat database has grown to include nucleotide sequences, sequences of T cell receptors for antigens (TCR), major histocompatibility complex (MHC) class I and II molecules and other proteins of immunological interest. It has been used extensively by immunologists to derive useful structural and functional information from the primary sequences of these proteins. An overall view of the Kabat Database and its various applications are summarized here. The Kabat Database is freely available at http://immuno.bme.nwu.edu

INTRODUCTION

The purpose of maintaining the Kabat Database of aligned sequences of proteins of immunological interest, in our opinion, is to provide useful correlations between structure and function for this special group of proteins from their nucleotide and amino acid sequences to their tertiary structures (1). These sequences are thus aligned with the ultimate aim of understanding how these proteins are folded and how they can perform their biological functions. We include only coding region sequences that have been published. In some cases, only the amino acid sequences were published, while the corresponding nucleotide sequences were deposited in GenBank. All stored sequences were then printed out and checked visually against available published sequences. We routinely survey for possible new sequences in journals in our libraries, Medline entries, cross-references from other papers, and author notification; however, we may still miss some sequences. GenBank, on the other hand, contains a substantial number of unpublished sequences. If there are doubts about these sequences or their annotations, please refer to the original papers. The Kabat numbering systems (see the Introduction of 2) for antibody light and heavy chains, for TCR alpha and beta chains, etc., go hand-in-hand with variability calculations. The locations of the CDRs are the theoretically derived positions which can be verified experimentally. Indeed, from the first antigen–antibody Fab complex (3) to the complexes of TCR, processed peptide and MHC class I molecule (4,5), it has been realized that alignment of amino acid sequences and variability calculations can be of utmost importance in understanding how these important macromolecules function biologically. Due to the rapid development of genetic and protein engineering methods, mouse and rat antibodies have been humanized to treat human cancers, viral infections, etc (6). CDRs of selected rodent antibodies are cut out and glued onto human antibody frameworks to minimize rejection by human patients.

Our predicted CDRs are slightly different from Chothia's. A careful comparison can be found from a hyperlink on our website to 'Andrew's Antibody Page' (http://www.biochem.ucl.ac.uk/~martin/abs/index.html).

Massive amounts of sequence data are being continuously published in the scientific literature. It is imperative to collect and properly align the sequences so that they can be used by as many researchers in this field as possible. We have previously published five editions of these sequences (see the Introduction of 2). In 1991, the fifth edition (2) consisted of three volumes. Currently, the database is more than five times as large. As of September 29, 1999, the Kabat database contained 1 599 375 and 2 517 756 nt for antibody light and heavy chain variable regions, respectively, as compared to 272 244 and 418 962 nt in 1991. Total numbers of entries, amino acids and bases of other categories of sequences can be obtained by using the 'Current Counts' hyperlink on our website. The collection is available on our website (http://www.immuno.bme.nwu.edu) which is free due to the generous support by various research grants from NIH since 1970.

Finally, numerous scientific papers have cited our database, quoting our fourth edition (7), fifth edition (2), or one of our more recent papers (8). On our part, we have been analyzing

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the Kabat Database during the past few years with reference to the total numbers of antibody and TCR V-genes, possible evolutionary selection processes, importance of antibody CDRH3s as related to their fine specificities, etc.

KABAT DATABASE

The Kabat Database may be accessed for searching, sequence retrieval and analysis by a few different methods: electronic mail, WWW and ftp. The electronic mail interface has been available since 1993, the WWW interface since 1995 and various formats of the database in electronic format for nearly a decade (8). Our data formats, searching tools, output formats and database structures have gradually been adopted by other immunological databases and interfaces.

Electronic mail interface

An electronic mail interface (seqhunt2@immuno.bme.nwu.edu) provides a non-interactive method for searching and sequence retrieval (9). Sending mail to the server address with the single word 'help' (no quotes) in the message body returns instructions for using the server.

All sequences classes are searchable and returnable. The query format allows making AND/OR/NOT constructed restrictions on the database and amino acid and nucleotide sequence pattern matching with allowable differences. Requests are processed as they are received and depending on the network traffic, take ~1–2 min to be searched and returned to the sender. The returned format is a fixed-line length record of 80 or fewer characters per line for ease in visual inspection and processing by user-written scripts or programs. The characters are plain text.

The query format for the sent request consists of two parts. The first part contains directives for the server to follow while the second part contains specifications of the search. Specification of the extent of data returned, the number of documents to return, starting document and whether plain ASCII text or PostScript should be used in the return format may be entered. Further, one can direct the server to return a distribution, the variability or unaligned raw data for the search specified.

The second part of the query contains the search restrictions on the database. Words separated by AND and OR may be used, as well as searching functions, like nucleotide/amino acid pattern matching and positional restriction matching.

There are basically three steps in translating and performing a search on the Kabat Database: generate the question or query, translate it into a format the server can recognize and decide on the output options desired of the returned matches. For example, if matches of mouse kappa light chains of anti-phosphorylcholine antibodies are desired, the query and restriction on the database would be:

Begin
@mouse and kappa and phosphorylcholine

The '@' before mouse tells the server that matches of the species mouse are desired, rather than searching through the entire database record for instances of the word 'mouse'. More complicated restrictions can be generated using parentheses for grouping and the minus sign '–' for NOT. Finding all rat and rabbit sequences which are not kappa light chains, and returning them as amino acid sequences in PostScript format would be constructed as:

PSAA
Begin
(rat and rabbit) and –kappa

Pattern matching is interpreted as the second part of an AND statement, such that finding all rat and rabbit sequences which are not kappa and contain the nucleotide pattern cagtacgtcag with three allowable mismatches, would be sent as:

Begin
(rat and rabbit) and –kappa [implicit AND]
#NM 3
cagtacgtcag

More examples of searching and output options may be found in the 'help' file returned from the server.

WWW interface

The WWW interface (8) to the Kabat Database: http://immuno.bme.nwu.edu contains searching and analysis tools as well as links to database download sites and other interesting databases. Most of the features found in the electronic mail interface are found in the WWW interface, as well as other tools. The WWW interface is more interactive than the Email and returns results faster, depending on the network traffic.

Searching and analysis tools

SeqhuntII. This grouping of programs allows searches through the annotations and sequence pattern matching of the amino acid and nucleotide sequence data with allowable mismatches. Like the Email server, restrictions on the database may be formulated as AND/OR/NOT constructs. Output extent, output format, maximum documents and starting document may be specified. Browsing of the output results in HTML format allows the user to view the database entries in an easy-to-read format. ASCII text may be selected as output for use in user-generated scripts and programs. PostScript generation allows for printing on a PostScript supporting printer. Sequence matching is returned aligned with the target sequence with nucleotide or amino acid differences from the database sequence displayed in a case change. Since the database contains only coding regions of genes and proteins, the query sequence should be a portion of the coding region being sought.

Variability. Variability and amino acid distributions of sequence groups may be generated for restrictions on the database. The variability plots are in PostScript format and may either be viewed on the screen with an appropriate PostScript viewer (e.g. GNU ghostscript or ghostview) or printed to a postscript-supporting printer. Plots for human and mouse TCR gamma and delta chain variable regions are shown in Figure 1. Scaling of the variability plots may be done allowing comparison of variability plots for different groupings of sequences. Distributions of the amino acids per position may be returned also, including the calculated variability for each position.

Sequence alignment. Alignment of user-entered coding regions of immunoglobulin light chains according to the Kabat numbering system can be performed. Because of the relatively few alignment options available for light chains, most sequences can be aligned. One can start with around 10 amino acid residues or 30 nt. There is no lower limit on the length of sequence to be matched. In some cases though, visual inspection and alignment is necessary, as is for heavy chain alignment,

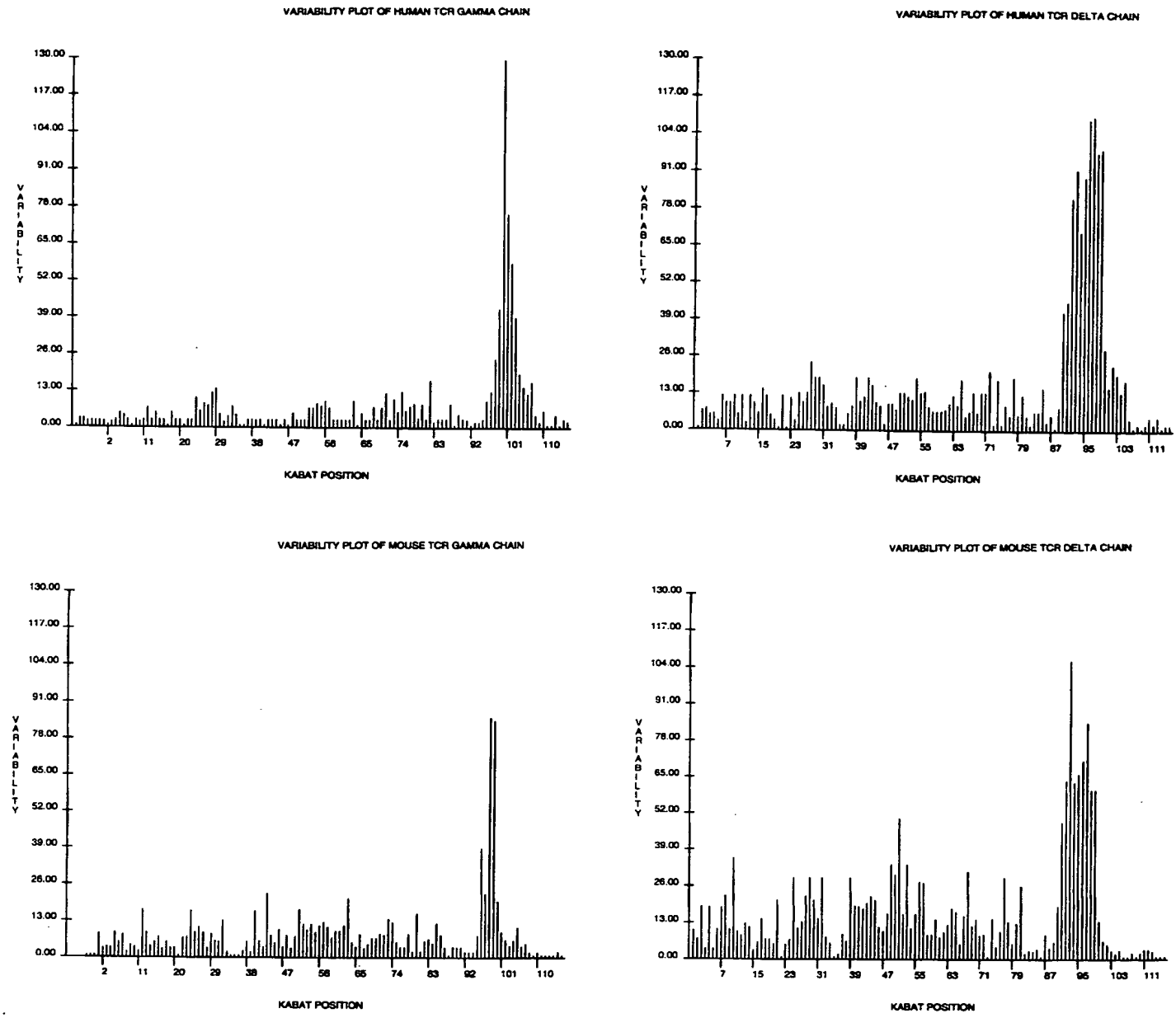

Figure 1. Variability plots for human and mouse TCR gamma and delta chain variable regions, using 377 human gamma, 1260 human delta, 297 mouse gamma and 461 mouse delta partial and complete sequences.

especially within the CDRH3 region, if additional codons or residues are inserted and denoted by '#'. If a suitable alignment counterpart from the database is not found for the target sequence, the user can contact us.

FTP. Various formats of the database are available for download from NCBI's repository under the directory 'kabat'. Currently active formats include a FASTA-like raw sequence format and the database's fixed length format of 80 or fewer characters per line and vertical alignment. Four main variations on the fixed length format exist to properly visually display single translations, pseudogene translations, J-minigenes and D-minigenes. Other immunological databases have adopted similar formats as exemplified by the three letter code amino acid translation followed by single letter code. A 'dump' version of the database is periodically updated which contains unlimited line length records more suitable for mass processing on unix-based systems.

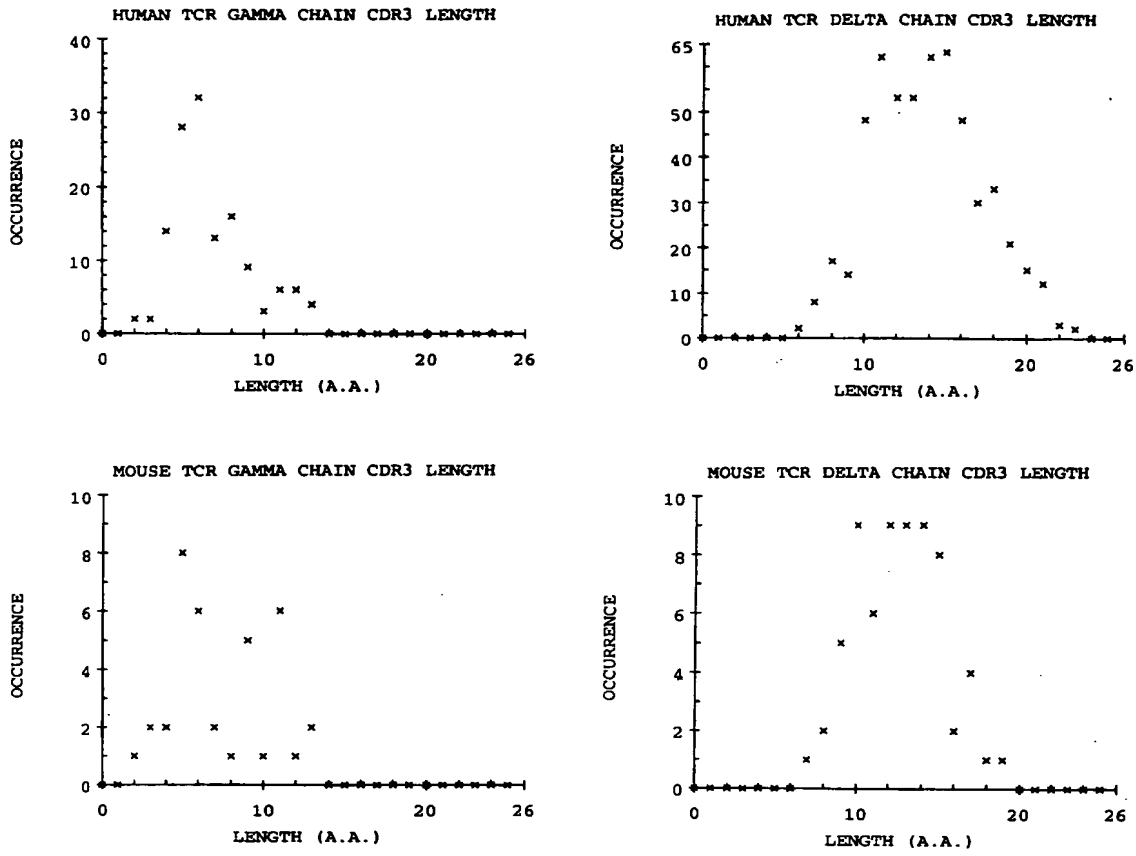

Figure 2. Length distributions of CDR3s of human and mouse TCR gamma and delta chains, based on 135 human gamma, 546 human delta, 37 mouse gamma and 66 mouse delta complete CDR3 sequences.

OTHER APPLICATIONS

As mentioned before, the Kabat Database was initially constructed for the purpose of identifying the antibody combining site (1). Starting from aligned amino acid sequences and using variability calculations, we have identified CDRs of antibody light and heavy chains, as well as those of TCRs. Such calculations can also provide useful predictions for MHC class I and II sequences (8), and to other aligned proteins sequences, e.g. HIV gp120, gp41, etc.

The importance of CDRH3 to confer fine specificity to antibodies was realized a few years ago (10). Furthermore, the unique CDRH3 nucleotide sequences have recently been used as a sensitive diagnostic test to detect residue B cell malignancies in cancer patients. Thus, many of these sequences have been determined. But most of them have been excluded from GenBank due to their relative short lengths. We have been meticulously collecting them, and realized the importance of their length distributions in antibodies of various specificities (11), and possible differences between CDRH3s of human and mouse (12). In the case of rabbit, the CDRH3s have less length variation than human and mouse. This may be compensated by the length variations of the CDRL3s (13).

The length variations of TCR alpha and beta chain CDR3s are very restricted (14). On the other hand, TCR gamma and delta chain CDR3s have more length variation, close to those of antibody heavy chains (Fig. 2). Whether they bind antigens directly is unclear.

During recent years, various research groups have decided to sequence the entire coding region of different antibody and TCR V-genes, in order to have an idea of their total numbers. On the other hand, we have discovered that pair-wise comparisons of V-gene nucleotide sequences in the Kabat Database provide very accurate estimations of their total numbers (15,16). In addition, such comparisons seem to suggest that antibody and TCR V-genes have evolved under different selective pressures (17). In the case of MHC class I sequences, comparison of their aligned sequences has elucidated a new mechanism of generating novel MHC class I molecules by random assortment of their a1 and a2 gene segments (18).

DISCUSSION

The Kabat Database has been around for 30 years. It has provided the immunology community a useful service, since it

not only is a sequence database but also incorporates vital aspects of the biology of the immune system. Various analytical methods have been developed to study the structure and function relations of proteins of immunological interest.
Electronic addresses:
http://immuno.bme.nwu.edu
seqhunt2@immuno.bme.nwu.edu
Citing the Kabat Database:
Authors using this database may cite this paper together with the electronic addresses.

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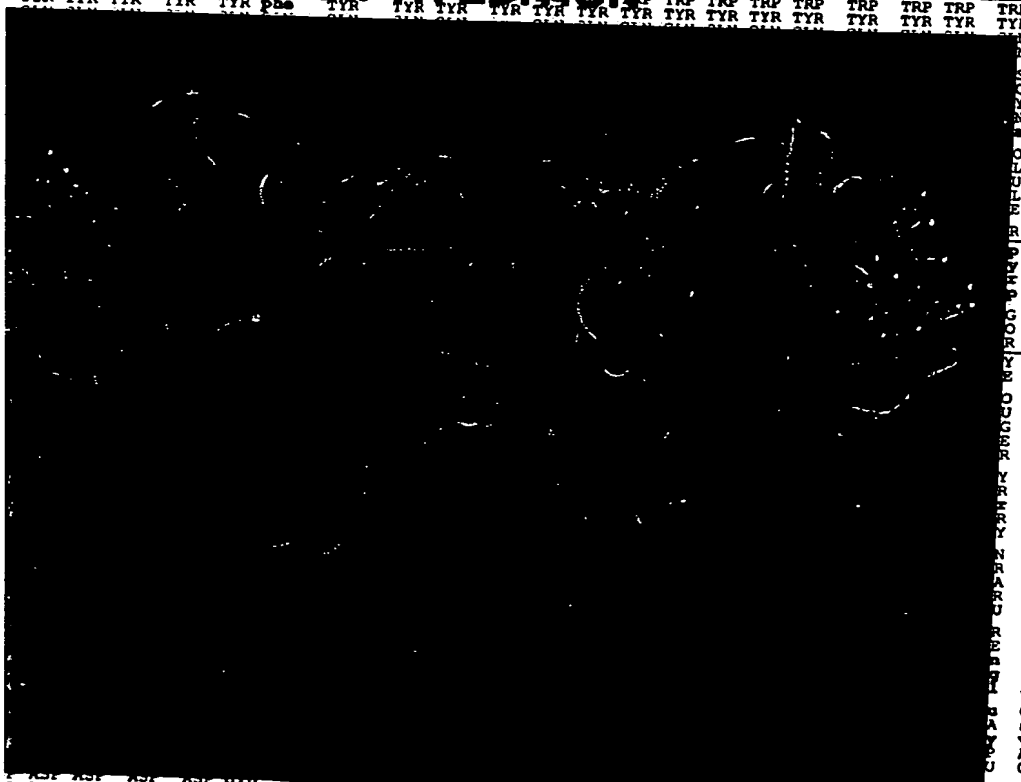
SEQUENCES OF PROTEINS OF IMMUNOLOGICAL INTEREST

VOL. II

FIFTH EDITION



1991

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

Kabat

In Fig. 1 and in the stereomodels of antibody combining sites, the location of the allotypic regions may clearly be seen to be on the outside of V_H away from the combining site. Residues 9 and 65 of V_H are numbered and will facilitate location of the V_Ha allotypes. The few cDNA sequences available in 1984 (65) provided no evidence that germ line sequences encoding latent allotypes may exist in some rabbits. Since then, additional germline and expressed V_Ha sequences (63-65,188,204-206) have further refined the information on V_Ha allotypes and V_Ha^- sequences. Newer analyses of germline V_H genes of rabbits have provided examples of potential genes and pseudogenes which could generate latent allotype sequences by somatic gene conversion mechanisms (187,199,203-208). Antisera to rabbit V_Ha allotypes crossreact with human IgG, various other species of IgM and IgG, and with the Galapagos shark 7S immunoglobulin and correlate with the N-terminal amino acid sequence (209,210).

It is becoming of great importance, with all of the different mechanisms which are clearly generating diversity, to evaluate the extent to which each type of diversity, other than those resulting in pseudogenes, contributes noise rather than functional differences in complementarity of antibody combining sites (70, 211).

Ohno et al. (212,213) have proposed that the genes coding for variable domains of the light and heavy chains arose from tandem repeats of a primordial nucleotide sequence about 48 base pairs in length which subsequently diverged by mutations and deletions producing a resemblance to FR1, FR2, and FR3. The complementary strand of the primordial 48 base pair repeat of V_L became the primordial V_H. The finding (147) that the complementary strands of the human D2 and D4 minigenes coded for a portion of CDR1 of V_κ tends to support this hypothesis. A 45 base pair primordial building block has also been proposed for the gene for the class I major histocompatibility complex (214).

The format of our precursor, V-region, C region sequences etc. of antibodies and T cell receptors has proven very useful in selecting primers for the polymerase chain reaction (215-217).

Constant Region Sequences

The constant region sequences were aligned in such a manner as to permit various comparisons of the light chain (C_L) and the individual domains of the heavy chain (C_H1, C_H2, C_H3, and C_H4). This was accomplished by sequential numbering on the left with gaps inserted for alignment. The following numbering system is used:

108 to 215 of C_L;
114 to 223 of C_H1, plus the first part of hinge (224 to 241), the end of hinge (242 and 243), and the first two residues of CH2 (244 and 245);
246 to 360 of C_H2;
361 to 496 of C_H3;
497 to 628 of C_H4.

The gene quadruplication in the human IgG3 hinge region (218) is numbered differently using letters 241A to 241Z, and 241AA to 241SS, and these residues should not be used in aligning domains for homology. The next two columns in the heavy chain tables indicate the EU (67) and OU (219) residue numbers, respectively. The succeeding columns which are numbered give the sequence data. The C_H and hinge domains conform to the findings of Sakano et al. (220), who defined each domain precisely by sequencing the coding and intervening nucleotide sequences bordering each domain.

The extensive nucleotide sequence data on exons for the constant regions of heavy chains have provided exact boundaries for C_H1, hinge, C_H2, C_H3, and C_H4. Usually the introns separating these domains fall within the codon for a single amino acid. We have included that amino acid residue with the domain, the exon of which contains two of the three coding nucleotides. The constant regions

of heavy chains thus contain four domains: C_H1, hinge, C_H2, and C_H3, or in IgM and IgE C_H1, C_H2, C_H3, and C_H4. Several C_H3 domains are extra long. These have been listed in a separate table after C_H3. An additional table is included to list several C_H4 domains that are very long and the C-terminal portions of membrane bound segments. Such extra long sequences in C_H3, C_H4, and membrane bound segments are listed retaining their individual protein numbers.

There are substantial species differences between the human, rat and rabbit C_κ allotypes. The amino acid sequences of rabbit C_κ allotypic determinants K-1, b4, b5 and b9 differ at 47 of 106 positions, the differences occurring in clusters; the K-2bas isotype differs at three additional positions (221) whereas the human Cκ allotypes differ by two positions (222) and the rat R1-1a and R1-1b differ at 11 positions (223).

The Fc receptors (224,225) are members of the immunoglobulin superfamily and provide the mechanism for interactions involving the constant regions of immunoglobulins binding to both immune complexes and antibodies (226-232). There are receptors for all classes which have arisen from a common precursor to diversify functionally. Fc receptors for a given Ig may have different affinities; thus there are high and low affinities for IgE. Fc RI and FcRIII have been shown to consist of non covalently associated complexes (cf. 224-225).

KAPPA LIGHT CONSTANT CHAINS

INVARIANT RESIDUES	1 HKLC 'CL #	2 ROY	3 AG	4 EU	5 DEN	6 BI	7 GM131 'CL	8 NIM	9 CUM	10 TI	11 MKLC 'CL #	12 17/9 'CL	13 MOPC 70	14 MOPC 321	15 MOPC 173	16 MOPC 41'CL	17 MOPC 41	18 K-MS 'CL	19 CEA 66-E3 'CL #	20 C.C58 M75 'CL	21 MOPC 21
107A	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
108		ARG						ARG	ARG	ASP							ARG				
109		THR	ARG THR	GLY THR	ARG THR	ARG THR	THR	THR	THR	THR	ALA	ARG ALA	ARG ALA	ARG ALA	ARG ALA	ALA	ALA	ALA	ALA	ARG ALA	ARG ALA
109A	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
110		VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	ASP	ASP	ASX	ASX	ASX	ASP	ASX	ASP	ASP	ASP	ASP
111		ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA
112		ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA
113	PRO(.99)	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO
114		SER	SER	SER	SER	SER	SER	SER	SER	SER	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR
115	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL
116		PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER
117		ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE
118		PHE	PHE	PHE	PHE	PHE	ILE	PHE	PHE	PHE	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO
119	PRO(.97)	PRO	PRO	PRO	PRO	PRO	PHE	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO
120	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO
121		SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER
122		ASP	ASP	ASN	ASP	ASP	ASP	ASP	ASP	ASP	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER
123		GLU	GLU	GLU	GLU	GLU	GLU	GLU	GLU	GLU	GLU	GLU	GLX	GLX	GLX	GLU	GLU	GLU	GLU	GLU	GLU
124		GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	---	---	---	---	---	---	---	---	---
124A	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
125		LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU
126		LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR
127		SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	GLY	GLY	GLY	SER	GLY	SER	SER	SER	SER
128		GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY
129		THR	THR	THR	THR	THR	THR	THR	THR	THR	GLY	GLY	SER	GLY	GLY	GLY	SER	GLY	GLY	GLY	GLY
130		ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA
131		SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER
132		VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL
133	VAL(.95)	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL
134	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS
135		LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE
136		LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU
137		ASN	ASN	ASN	ASP	ASN	ASN	ASN	ASN	ASN	ASN	ASN	ASX	ASN	ASX	ASN	ASN	ASN	ASN	ASN	ASN
138		ASN	ASN	ASN	ASP	ASN	ASN	ASN	ASN	ASN	ASN	ASN	ASX	ASN	ASX	ASN	ASN	ASN	ASN	ASN	ASN
139		PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE
140		TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	LEU	LEU	LEU	PHE	LEU	PHE	PHE	PHE	PHE
141	PRO	PRO	PRO	PRO	PRO	PRO	ARG	PRO	PRO	PRO	PRO	PRO	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS
142		ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG	LYS	LYS	ASP	ASP	ASP	ASX	ASP	ASP	ASP	ASP	ASP
143		GLU	GLU	GLU	GLU	GLU	GLU	GLU	GLU	GLU	ASP	ASP	---	---	---	---	---	---	---	---	---
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145		LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	ASN	ASN	ASN	ASN	ASN	ASN	ASN	ASN	ASN	ASN	ASN
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147	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
148		GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS
149	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP
150		LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS
		VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE
151	ASP(.95)	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
152		ASP	ASP	ASP	ASP	ASP	ASP	ASN	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP
		ASN	ASN	ASN	ASN	ASN	ASN	ASP	ASN	ASN	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY
153	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
		ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER
154		LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	GLU	GLU	GLU	GLU	GLU	GLU	GLU	GLU	GLU	GLU	GLU
155		GLN	GLN	GLN	GLN	GLN	GLN	GLN	LEU	LEU	ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG
156		SER	SER	SER	SER	SER	SER	SER	GLN	GLN	GLN	GLN	GLX	GLN	GLX	GLN	GLN	GLN	GLN	GLN	GLN
157		GLY	GLY	GLY	GLY	GLY	GLY	GLY	SER	SER	ASN	ASN	ASX	ASN	ASX	ASN	ASN	ASN	ASN	ASN	ASN
158		ASN	ASN	ASN	ASN	ASN	ASN	ASN	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY
159		SER	SER	SER	SER	SER	SER	SER	SER	SER	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL
160		GLN	GLN	SER	GLN	GLN	GLN	GLN	GLN	GLN	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU
161		GLU	GLU	GLU	GLU	GLU	GLU	GLU	GLU	GLU	ASN	ASN	GLX	ASN	LEU	ASN	ASN	ASN	ASN	ASN	ASN
162		SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	ASX	SER	SER	SER	SER	SER	SER	SER	SER
163		VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	TRP	TRP	SER	ASN	ASN	TRP	TRP	TRP	TRP	TRP	TRP
164		THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	ASX	THR	THR	THR	THR	THR	THR	THR	THR
165		GLU	GLN	GLU	GLU	GLU	GLX	GLN	GLU	GLN	GLN	GLN	TRP	GLU	ASP	GLU	ASP	ASP	ASP	ASP	ASP
166		GLN	GLN	GLN	GLN	GLN	GLX	GLN	GLN	GLN	GLN	GLN	ASX	TRP	GLN	ASP	GLN	GLN	GLN	GLN	GLN
167		ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	SER	ASP	ASP	GLN	ASP	ASP	ASP	ASP	ASP
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170		ASP	ASP	ASP	ASP	ASP	---	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP
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176	SER	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	MET	MET	MET	MET	MET	MET	MET	MET	MET	MET	MET
177	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER
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184		ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ASP	ASP	ASX	ASP	ASP	GLU	ASP	ASP	ASP	ASP	ASP
185		ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	GLU	GLU	GLX	GLU	GLU	GLU	GLU	GLU	GLU	GLU	GLU
186		TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR
187		GLU	GLU	GLU	GLU	GLU	GLU	GLU	GLU	GLU	GLU	GLU	GLX	GLU	GLU	GLU	GLX	GLU	GLU	GLU	GLU
188	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
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190		HIS	HIS	HIS	HIS	HIS	HIS	HIS	HIS	HIS	HIS	HIS	HIS	HIS	HIS	HIS	HIS	HIS	HIS	HIS	HIS
191		LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	ASN	ASN	ASX	ASN	ASN	ASN	ASX	ASN	ASN	ASN	ASN
192		VAL	LEU	VAL	VAL	VAL	VAL	VAL	VAL	VAL	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER
193		TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR
194		ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR
	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS
195		GLU	GLU	GLU	GLU	GLU	GLU	GLU	GLU	GLU	GLU	GLU	GLX	GLU	GLU	GLU	GLX	GLU	GLU	GLU	GLU
196		VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA
197		THR	THR	THR	THR	THR	THR	THR	THR	THR	---	---	---	---	---	---	---	---	---	---	---
198	HIS	HIS	HIS	HIS	HIS	HIS	HIS	HIS	HIS	HIS	HIS	HIS	HIS	HIS	HIS	HIS	HIS	HIS	HIS	HIS	HIS
199		GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS
200		GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR
201		LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER
202		SER	SER	SER	SER	SER	SER	SER	SER	SER	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR
203		PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER
204		---	---	---	---	---	---	---	---	---	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO
205	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
206		VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE
206A		THR	THR	THR	THR	THR	THR	THR	THR	THR	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL
207	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
208		LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS
219		SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER
210		PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE
211	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
212		ASN	ASN	ASN	ASN	ASN	ASN	ASN	ASN	ASN	ASN	ASN	ASN	ASN	ASN	ASN	ASN	ASN	ASN	ASN	ASN
213		ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG
214		GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	ASN	ASN	ASN	ASN	ASN	ASN	ASN	ASN	ASN	ASN	ASN
215	CYS	GLU	GLU	GLU	GLU	GLU	GLU	GLU	GLU	GLU	GLU	GLU	GLU	GLU	GLU	GLU	GLU	GLU	GLU	GLU	GLU
216		CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS
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KAPPA LIGHT CONSTANT CHAINS (cont'd)

	22 LOU'CL (RI-1B) #	23 Y3-Ag 1.2.3. 'CL	24 DA'CL (RI-1A) #	25 S 211	26 LEW	27 DA	28 IR-102	29 IR-52	30 R.I.C. 'CL	31 R.C. 'CL	32 RLL 'CL	33 RFC 'CL	34 RTT 'CL	35 RS 'CL	36 RV 'CL	37 RABBIT K1B4 'CL #	38 RABBIT K2B4 'CL	39 RABBIT K1B5 'CL	40 RABBIT K1B4 VAR'CL	41 RABBIT B9'CL	42 RABBIT K2b6 'CL
107A	---	---	---	---	---	---			---	---	---	---	---	---	---	---	---	---	---	---	
108	---	---	---	ARG	ARG	ARG			---	---	---	---	---	---	---	---	---	---	---	---	
109	ALA	ALA	ALA	ALA	ALA	ALA			ALA	ALA	ALA	ALA	ALA	ALA	ALA	GLY	ARG	VAL		CYS	
109A	---	---	---	---					---	---	---	---	---	---	---	ASP	ASP	ALA	ASP	ASP	ASP
110	ASP	ASP	ASP	ASN					ASP	ASP	ASP	ASP	ASP	ASP	ASP	---	---	---	---	PRO	---
111	ALA	ALA	ALA	ALA					---	---	---	---	---	---	---	PRO	PRO	THR	PRO	PRO	PRO
112	ALA	ALA	ALA	ALA					ALA	ALA	ALA	ALA	ALA	ALA	ALA	VAL	VAL	LEU	VAL	ILE	VAL
113	PRO	PRO	PRO	PRO					ALA	ALA	ALA	VAL	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA
114	THR	THR	THR	THR					PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO
115	VAL	VAL	VAL	VAL					THR	THR	THR	THR	THR	THR	THR	THR	SER	THR	THR	THR	SER
									VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL
116	SER	SER	SER	SER					SER	SER	SER	SER	SER	SER	SER	LEU	LEU	LEU	LEU	LEU	LEU
117	ILE	ILE	ILE	ILE					ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	LEU	ILE	ILE	LEU	LEU
118	PHE	PHE	PHE	PHE					PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE
119	PRO	PRO	PRO	PRO					PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO
120	PRO	PRO	PRO	PRO					PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO
121	SER	SER	SER	SER					SER	SER	SER	SER	SER	SER	SER	ALA	SER	SER	SER	SER	SER
122	THR	THR	MET	THR		MET			SER	SER	SER	SER	SER	SER	SER	ALA	LYS	PRO	ALA	ALA	LYS
123	GLU	GLU	GLU	GLX		GLX			ASP	GLU	GLU	GLU	GLU	GLU	GLU	ASP	GLU	ALA	ASP	ASP	GLU
124	GLN	GLN	GLN	GLX		GLX			GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLU	GLU	LEU	GLN	GLU
124A	---	---	---	---		---			---	---	---	---	---	---	---	---	---	---	---	---	---
125	LEU	LEU	LEU	LEU		LEU			---	---	---	---	---	---	---	---	---	---	---	---	---
126	ALA	ALA	THR	ALA		THR			LEU	LEU	LEU	LEU	LEU	LEU	LEU	VAL	LEU	LEU	VAL	LEU	LEU
127	THR	THR	SER	THR		SER			ALA	ALA	ASP	ALA	ALA	ALA	ALA	ALA	THR	ALA	ALA	THR	THR
128	GLY	GLY	GLY	GLY		GLY			THR	SER	THR	THR	THR	ALA	SER	THR	THR	THR	THR	THR	THR
									GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLU	GLY	GLY
129	GLY	GLY	GLY	GLY		GLY			GLY	GLY	GLY	GLY	SER	GLY	GLY	THR	THR	THR	THR	THR	THR
130	ALA	ALA	ALA	ALA		ALA			ALA	ALA	ALA	ALA	ALA	ALA	ALA	VAL	ALA	ALA	VAL	VAL	ALA
131	SER	SER	THR	SER		THR			SER	SER	SER	SER	SER	SER	SER	THR	THR	THR	THR	THR	THR
132	VAL	VAL	VAL	VAL		VAL			VAL	VAL	VAL	VAL	VAL	VAL	VAL	ILE	ILE	ILE	ILE	ILE	ILE
133	VAL	VAL	VAL	VAL		VAL			VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL
134	CYS	CYS	CYS	CYS	CYS	CYS			CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS
135	LEU	LEU	PHE	LEU	LEU	PHE			ILE	PHE	PHE	PHE	PHE	PHE	PHE	VAL	VAL	VAL	VAL	VAL	VAL
136	MET	MET	VAL	MET	MET	VAL	MET	MET	MET	ILE	ILE	ILE	VAL	VAL	VAL	ALA	ALA	ALA	ALA	ALA	ALA
137	ASN	ASN	ASN	ASN	ASN	ASN	ASN	ASN	ASN	ASN	ASN	ASN	ASN	ASN	ASN	ASN	ALA	ASN	ASN	ASN	ASN
138	ASN	ASN	ASN	LYS	ASX		ASN	ASN	ASN	LYS	ASN	ASN	ASN	ASN	GLY	LYS	LYS	LYS	LYS	LYS	LYS
139	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	TYR	PHE	TYR	TYR	PHE	PHE
140	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	GLY	PHE	TYR	PHE	PHE	ARG	TYR
141	PRO	PRO	PRO	PRO	PRO		PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO
142	ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG	LYS	ARG	LYS	LYS	LYS	LYS	ASP	SER	ASP	ASP	ASN	SER
143	ASP	ASP	ASP	ASP	ASX	ASX	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	VAL	ASP	GLY	VAL	ASP	ASP
144	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	---	ILE	---	---	ILE	ILE
145	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	THR	THR	THR	THR	THR	THR
146	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	LEU	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL
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147	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	THR	THR	THR	THR	THR	THR
148	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP
149	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	GLU	LYS	GLN	GLU	LYS	LYS
150	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	VAL	VAL	VAL	VAL	VAL	VAL
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151	ASP	ASP	ASP	ASP	ASP	ASP	ASX	ASX	---	---	---	---	---	---	---	---	---	---	---	---	---
152	GLY	GLY	GLY	GLY		GLY	GLY	GLY	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP
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153	THR	THR	SER	THR		THR	THR		---	---	---	---	---	---	---	---	---	---	---	---	---
154	GLU	GLU	GLU	GLU		GLU	GLX	GLX	SER	SER	SER	SER	SER	SER	SER	THR	THR	LYS	THR	GLU	THR
155	ARG	ARG	GLN	ARG		GLX	ARG	ARG	GLU	GLU	GLU	GLU	GLU	GLU	GLU	THR	THR	PRO	THR	ILE	THR
156	ARG	ARG	ARG	---	ARG	ARG	---	---	ARG	ARG	ARG	ARG	ARG	ARG	ARG	GLN	GLN	LEU	GLN	GLN	GLN
157	ASP	ASP	ASP	ASX		ASX	ASX	ASX	GLN	ARG	GLN	GLN	GLN	GLN	GLN	THR	GLN	THR	THR	GLN	GLN
158	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	ASP	ASN	ASP	ASN	ASN	ASN	ASN	THR	SER	THR	THR	SER	SER
									GLY	ASP	GLY	ASP	ASP	ASP	ASP	GLY	GLY	GLY	GLY	GLY	GLY
159	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	ILE	VAL	VAL	VAL	VAL	ILE	ILE	ILE	ILE	ILE	ILE
160	LEU	LEU	LEU	LEU			LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	GLU	GLU	GLU	GLU	GLU	GLU
161	ASP	ASP	ASP	ASX			ASX	ASX	ASP	ASN	ASP	ASN	ASN	ASN	ASN	ASN	THR	ASN	ASN	ASN	ASN
162	SER	SER	SER	SER			SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER
163	VAL	VAL	VAL	VAL			VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	LYS	LYS	LYS	THR	LYS	LYS
164	THR	THR	THR	THR		THR	THR		THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR
165	ASP	ASP	ASP	ASX		ASX	ASX		ASP	ASP	ASP	ASP	ASP	ASP	ASP	PRO	PRO	PRO	PRO	PRO	PRO
166	GLN	GLN	GLN	GLX		GLX	GLX		GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN
167	ASP	ASP	ASP	ASX		ASX	ASX		ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASN	ASN	ASN	SER	SER	SER
168	SER	SER	SER	SER		SER			SER	SER	SER	SER	SER	SER	SER	SER	PRO	SER	SER	PRO	PRO
169	LYS	LYS	LYS	LYS	LYS	LYS	LYS		LYS	LYS	LYS	LYS	LYS	LYS	LYS	ALA	GLU	ASP	ALA	GLU	GLU
170	ASP	ASP	ASP	ASP			ASX		ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP
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171	SER	SER	SER	SER					---	---	---	---	---	---	---	---	---	---	---	---	---
									SER	SER	SER	SER	SER	SER	CYS	ASN	CYS	CYS	CYS	ASN	
172	THR	THR	THR	THR					THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR
173	TYR	TYR	TYR	TYR					TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR
174	SER	SER	SER	SER					SER	SER	SER	SER	SER	SER	SER	SER	ASN	ASN	ASN	SER	SER
175	MET	MET	MET	MET					MET	MET	MET	MET	MET	MET	MET	LEU	LEU	LEU	LEU	LEU	LEU
176	SER	SER	SER	SER					SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER
177	SER	SER	SER	SER					SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER
178	THR	THR	THR	THR					THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR
179	LEU	LEU	LEU	LEU					LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU
180	SER	SER	SER	SER					THR	THR	THR	THR	THR	THR	THR	THR	SER	THR	THR	SER	SER
181	LEU	LEU	LEU	LEU					THR	THR	THR	THR	THR	THR	THR	LEU	LEU	LEU	LEU	LEU	LEU
									LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU
182	THR	SER	THR	THR					THR	THR	ASN	THR	THR	THR	THR	THR	THR	LYS	THR	THR	THR
183	LYS	LYS	LYS	LYS					LYS	LYS	LYS	LYS	LYS	LYS	LYS	SER	SER	SER	LYS	SER	SER
184	ALA	ALA	VAL	ALA	ALA	VAL			ALA	ALA	ALA	ALA	ALA	ALA	ALA	THR	ALA	ASP	THR	ALA	ALA
185	ASP	ASP	GLU	ASP	ASP	GLX			ASP	ASP	ASP	ASP	ASP	ASP	ASP	GLN	GLN	GLU	GLN	GLN	GLN
186	TYR	TYR	TYR	TYR		TYR			TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR
187	GLU	GLU	GLU	GLN		GLN			GLU	GLU	GLU	GLU	GLU	GLU	GLU	ASN	ASN	ASN	ASN	ASN	ASN
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188	SER	SER	ARG	SER		ARG			---	---	---	---	---	---	---	---	---	---	---	---	---
189	HIS	HIS	HIS	HIS					SER	ARG	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER
									HIS	HIS	HIS	HIS	HIS	HIS	HIS	HIS	HIS	HIS	HIS	HIS	HIS
190	ASN	ASN	ASN	ASN					ASN	ASN	ASN	ASN	ASN	ASN	LYS	SER	ASP	LYS	SER	SER	
191	LEU	LEU	LEU	LEU					LEU	LEU	LEU	LEU	LEU	LEU	GLU	VAL	GLU	GLU	VAL	VAL	
192	TYR	TYR	TYR	TYR					TYR	TYR	PHE	PHE	PHE	PHE	TYR	TYR	TYR	TYR	TYR	TYR	
193	THR	THR	THR	THR					THR	THR	VAL	VAL	VAL	VAL	THR	THR	THR	THR	THR	THR	
194	CYS	CYS	CYS	CYS					CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	
195	GLU	GLU	GLU	GLN	GLN	GLN			GLU	GLU	GLU	GLU	GLU	GLU	LYS	GLU	GLN	LYS	GLU	GLU	
196	VAL	VAL	VAL	VAL	VAL	VAL			VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	
197	VAL	VAL	VAL	VAL	VAL	VAL			VAL	VAL	VAL	VAL	VAL	VAL	THR	VAL	ALA	THR	VAL	VAL	
198	HIS	HIS	HIS	HIS	HIS	HIS			HIS	HIS	HIS	HIS	HIS	HIS	---	---	---	---	---	---	
199	LYS	LYS	LYS	LYS	LYS	LYS			LYS	LYS	LYS	LYS	LYS	LYS	GLN	GLN	GLN	GLN	HIS	GLN	
200	THR	THR	THR	THR	THR	THR			THR	THR	THR	THR	THR	THR	GLY	GLY	GLY	GLY	ASN	GLY	
201	SER	SER	SER	SER					SER	SER	SER	SER	SER	SER	THR	SER	SER	THR	SER	SER	
202	SER	SER	SER	SER					ALA	ALA	ALA	ALA	ALA	ALA	THR	ALA	GLY	THR	SER	GLY	
203	SER	SER	SER	SER					SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	
204	PRO	PRO	PRO	PRO					PRO	PRO	PRO	PRO	PRO	PRO	---	PRO	PRO	---	ALA	PRO	
205	VAL	VAL	VAL	VAL					VAL	VAL	VAL	ILE	VAL	VAL	VAL	ILE	VAL	VAL	ILE	ILE	
205A	---	---	---	TRP					VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	
206	LYS	LYS	LYS	LYS	LYS	LYS			---	---	---	---	---	---	---	---	---	---	---	---	
207	SER	SER	SER	ASN	SER	SER			LYS	LYS	LYS	LYS	LYS	LYS	LYS	GLN	GLN	GLN	GLN	GLN	
									SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	
208	PHE	PHE	PHE	PHE	PHE	PHE			PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	
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209	ASN	ASN	ASN	ASN	ASN				---	---	---	---	---	---	---	---	---	---	---	---	
210	ARG	ARG	ARG	ARG	ARG	ARG			ASN	ASN	ASN	ASN	ASN	ASN	ASN	ASN	SER	ASN	ASN	ASN	
									ARG	ARG	ARG	LYS	LYS	ARG	ARG	ARG	ARG	ARG	ARG	ARG	
211	ASN	ASN	ASN	ASN	ASN	ASN			ASN	ASN	ASN	ASN	ASN	ASN	GLY	GLY	LYS	GLY	GLY	GLY	
212	GLU	GLU	GLU	GLU	GLU	GLU			GLU	GLU	GLU	GLU	GLU	GLU	ASP	ASP	ASN	ASP	ASP	ASP	
213	CYS	CYS	CYS	CYS	CYS	CYS			CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	
214	---	---	---	---	---	---			---	---	---	---	---	---	---	---	---	---	---	---	
215	---	---	---	---	---	---			---	---	---	---	---	---	---	---	---	---	---	---	

KAPPA LIGHT CONSTANT CHAINS (cont'd)

	43 RABBIT K2b9 'CL	44 4135	45 4153 -I •	46 B9 POOL •	47 4539	48 B5 POOL	49 B5 POOL'	50 17D9 'CL	51 3C8 'CL	52 BAS C4R -47 'CL •	53 2699	54 C14 -4	55 1966	56 F20	57 B6 POOL	58 H628	59 6038 •	60 RANA CATES-BEIANA	61 CHIMPAN-ZEE CH4-25 'CL	62 SHARK HORNED 1301 'CL	63 SHARK HORNED 1501 'CL
107A		---		---		---		---	---	---	---		---	---		---	---	---	---	---	---
108		GLY		GLY		VAL		CYS	ARG	GLY	VAL		VAL	VAL		VAL	ASP	ARG	---	SER	SER
109	ASP	ASP	ASP	ASP	ASP	ALA		ASP	ASP	ASP	ALA		ALA	ALA		ASP	PRO	GLY	THR	SER	SER
109A	---	---	PRO	PRO	---	---		PRO	---	---	---		---	---		---	---	GLU	---	GLU	GLU
110	PRO	PRO	PRO	PRO	PRO	THR		PRO	PRO	PRO	THR		THR	THR		PRO	VAL	ASN	VAL	ASP	ASP
111	VAL	VAL	ILE	ILE	VAL	LEU		ILE	VAL	VAL	LEU		LEU	LEU		VAL		VAL	ALA	ARG	ARG
112	ALA	ALA	ALA	ALA	ALA	ALA		ALA	ALA	ALA	ALA		ALA	ALA		ALA	ALA	ARG	ALA	LYS	LYS
113	PRO	PRO	PRO	PRO	PRO	PRO		PRO	PRO	PRO	PRO	ALA	PRO	PRO		PRO	PRO	PRO	PRO	PRO	PRO
114	SER	THR	THR	THR	THR	THR		THR	SER	SER	THR	THR	THR	THR		PRO	SER	THR	SER	SER	SER
115	VAL	VAL	VAL	VAL	VAL	VAL		VAL	VAL	VAL	VAL	VAL	VAL	VAL		VAL	VAL	VAL	VAL	VAL	VAL
116	LEU	LEU	LEU	LEU	LEU	LEU		LEU	LEU	LEU	LEU	LEU	LEU	LEU		LEU	LEU	SER	PHE	LEU	LEU
117	LEU	ILE	LEU	LEU	ILE	ILE		LEU	LEU	LEU	ILE	ILE	ILE	ILE		ILE	LEU	ILE	ILE	LEU	LEU
118	PHE	PHE	PHE	PHE	PHE	PHE		PHE	PHE	PHE	PHE	PHE	PHE	PHE		PHE	PHE	TYR	PHE	LEU	LEU
119	PRO	PRO	PRO	PRO	PRO	PRO		PRO	PRO	PRO	PRO	PRO	PRO	PRO		PRO	PRO	CYS	PRO	PRO	PRO
120	PRO	PRO	PRO	PRO	PRO	PRO		PRO	PRO	PRO	PRO	PRO	PRO	PRO		PRO	PRO	PRO	PRO	PRO	PRO
121	SER	ALA	SER	SER	SER	ALA		SER	SER	SER	ALA	ALA	SER	SER		SER	SER	SER	SER	SER	SER
122	LYS	ALA	ALA	ALA	ALA	PRO		ALA	LYS	LYS	PRO	SER	SER	SER		PRO	LYS	LEU	ASP	SER	SER
123	GLU	ASP	ASP	ASP	ASP	ALA		ASP	GLU	GLU	ALA	ALA	ALA	ALA		ALA	GLU	GLU	GLU	GLU	GLU
124	GLU	GLN	GLN	GLN	LEU	GLN		GLN	GLU	GLU	GLN	GLN	GLU	GLU		ASP	GLU	GLN	GLN	GLU	GLU
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124A	---	---	---	---	---	---		---	---	---	---	---	---	---		---	---	---	---	---	---
125	LEU	VAL	LEU	LEU	VAL	LEU		LEU	LEU	LEU	LEU	LEU	LEU	LEU		LEU	LEU	ARG	LEU	ILE	ILE
126	THR	ALA	THR	THR	ALA	ALA		THR	THR	THR	ALA	ALA	ALA	ALA		ALA	THR	ASN	LYS	ASP	ASP
127	THR	THR	THR	THR	THR	THR		THR	THR	THR	THR	THR	THR	THR		THR	THR	SER	SER	SER	SER
128	GLY	GLY	GLX	GLX	GLY	GLY		GLU	GLY	GLY	GLY	GLY	GLY			GLY	GLY	GLY	GLY	GLY	GLY
129	THR	THR	THR	THR	THR	ALA		THR	THR	THR	ALA	THR	THR	THR		ASP	THR	SER	THR	TRP	TRP
130	ALA	VAL	VAL	VAL	VAL	VAL		VAL	ALA	ALA	VAL	VAL	ALA	ALA		ALA	ALA	ALA	ALA	ALA	ALA
131	THR	THR	THR	THR	THR	THR		THR	THR	THR	THR	THR	THR	THR		THR	THR	SER	SER	THR	THR
132	ILE	ILE	ILE	ILE	ILE	ILE		ILE	ILE	ILE	ILE	ILE	ILE			ILE	•	THR	VAL	LEU	LEU
133	VAL	VAL	VAL	VAL	VAL	VAL		VAL	VAL	VAL	VAL	VAL	VAL	VAL			VAL	VAL	VAL	SER	SER
134	CYS	CYS	CYS	CYS	CYS	CYS		CYS	CYS	CYS	CYS	CYS	CYS	CYS		CYS	CYS	CYS	CYS	CYS	CYS
135	VAL	VAL	VAL	VAL	VAL	VAL		VAL	VAL	VAL	VAL	VAL	VAL			VAL	VAL	LEU	LEU	LEU	LEU
136	ALA	ALA	ALA	ALA	ALA	ALA		ALA	ALA	ALA	ALA	ALA	ALA			ALA	ALA	VAL	LEU	VAL	VAL
137	ASN	ASN	ASN	ASN	ASN	ASN		ASN	ASN	ASN	ASN	ASN	ASN			ASN		ASP	ASN	SER	SER
138	LYS	LYS	LYS	LYS	LYS	LYS		LYS	LYS	LYS	LYS	LYS	LYS	LYS		LYS		LYS	ASN	HIS	ARG
139	PHE	TYR	PHE	PHE	TYR	TYR	TYR	PHE	PHE	PHE	TYR	TYR	TYR	TYR	TYR	TYR		PHE	PHE	PHE	PHE
140	TYR	PHE		ARG	PHE	PHE	PHE	ARG	TYR	TYR	PHE	PHE	PHE	PHE	PHE	PHE		TYR	TYR	LYS	LYS
141	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO		PRO	PRO	PRO	PRO
142	SER	ASP	ASP	ASP	ASP	ASP	ASP	ASN	SER	SER	ASP	ASP	ASP	ASP	ASP	ASP		GLY	ARG	GLY	GLY
143	ASP	VAL	ASP	ASP	VAL	GLY	GLY	ASP	ASP	ASP	GLY	GLY	GLY	GLY	GLY	VAL		GLY	GLU	PHE	PHE
144	ILE	---	ILE	ILE	---	---	---	ILE	ILE	ILE	---	---	---	---	---	---		ALA	ALA	VAL	VAL
145	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR		GLN	LYS	ARG	ARG
146	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL		VAL	VAL	VAL	VAL
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147	THR	THR		THR		THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR		THR	GLN	LEU	LEU
148	TRP	TRP		TRP		TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP		TRP	TRP	TRP	TRP
149	LYS	GLU		LYS		GLN	GLU	LYS	LYS	LYS	GLU	GLU	LYS	LYS	LYS	LYS		LYS	LYS	ARG	ARG
150	VAL	VAL		VAL		VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL			VAL	VAL	VAL
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151	ASP	ASP		ASP		ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP			ASP	ASP	ASP
152	GLY	GLY		ASP		GLY	GLY	ASP	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY			ASN	ASP	ASP
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153	THR	THR		GLU		LYS	LYS	GLU	THR	THR	LYS	LYS	ILE	THR		THR			ALA	LYS	LYS
154	THR	THR		ILE		PRO	PRO	ILE	THR	THR	PRO	PRO	THR	ILE		THR			LEU	GLU	GLU
155	GLN	GLN		GLN		LEU	LEU	GLN	GLN	GLN	LEU	LEU	GLN	GLN		GLN			GLN	THR	THR
156	GLN	THR		GLN		THR	THR	GLN	GLN	GLN	THR	THR	SER	SER		THR			SER	ASP	ASP
157	SER	THR		SER		THR	THR	SER	SER	SER	THR	THR	SER	SER		THR			GLY	SER	SER
158	GLY	GLY		GLY		GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY		GLY			ASN	GLY	GLY
159	ILE	ILE		ILE		ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE		ILE			SER	VAL	VAL
160	GLU	GLU		GLU		GLU	GLU	GLU	GLU	GLU	GLU	GLU	GLU	ASN		GLU			GLN	THR	THR
161	ASN	ASN		ASN		THR	THR	ASN	ASN	ASN	THR	THR	ASN	ASN					GLU	THR	THR
162	SER	SER		SER		SER	SER	SER	SER	SER	SER	SER	SER	SER					SER	GLY	GLY
163	LYS	LYS		THR		LYS	LYS	THR	LYS	LYS	LYS	LYS	LYS			LYS			VAL	THR	THR
164	THR	THR		THR		THR		THR	THR	THR	THR	THR	THR	THR		THR	THR		THR	VAL	VAL
165	PRO	PRO		PRO		PRO		PRO	PRO	PRO	PRO	PRO	PRO	PRO		PRO	PRO		GLU	SER	SER
166	GLN	GLN		GLN		GLN		GLN	GLN	GLN	GLN	GLN	GLN	GLN		GLN	GLN		GLN	THR	THR
167	SER	ASP		SER		ASN		SER	SER	SER	ASN	ASN	ASN	ASN		ASN	SER		ASP	ASP	ASP
168	PRO	SER		PRO		SER		PRO	PRO	PRO	SER	SER	GLY	GLY		SER	PRO		SER	SER	SER
169	GLU	ALA		GLU		ASP		GLU	GLU	GLU	ASP	ASP	ALA	ALA		ASP	GLU		LYS	ASP	ASP
170	ASP	ASP		ASP		ASP		ASP	ASP	ASP	ASP		ASP	ASP		ASP	ASP		ASP	GLN	GLN
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171	ASN	CYS		CYS		CYS		CYS	ASN	ASN	CYS		CYS	CYS		CYS	ASN		SER	---	---
172	THR	THR		THR		THR		THR	THR	THR	THR	THR	THR	THR		THR	THR		THR	THR	THR
173	TYR	TYR		TYR		TYR		TYR	TYR	TYR	TYR	TYR	TYR	TYR		TYR	TYR		TYR	TYR	TYR
174	SER	ASN				ASN		ASN	SER	SER	ASN	ASN	ASN	ASN		ASN	SER		SER	SER	SER
175	LEU	LEU		LEU		LEU		LEU	LEU	LEU	LEU	LEU	LEU	LEU		LEU	LEU		LEU	LEU	LEU
176	SER	SER		SER		SER		SER	SER	SER	SER	SER	SER	SER		SER	SER		SER	SER	SER
177	SER	SER		SER		SER		SER	SER	SER	SER	SER	SER	SER		SER	SER		SER	SER	SER
178	THR	THR		THR		THR		THR.	THR	THR	THR	THR	THR	THR		THR	THR		THR	TYR	TYR
179	LEU	LEU		LEU		LEU		LEU	LEU	LEU	LEU	LEU	LEU	LEU		LEU			LEU	LEU	LEU
180	SER	THR		SER		THR		SER	SER	SER	THR	THR	THR	THR		THR			THR	ARG	ARG
181	LEU	LEU		LEU		LEU		LEU	LEU	LEU	LEU	LEU	LEU	LEU		LEU			LEU	VAL	VAL
182	THR	THR		THR		GLN		THR	THR	THR	GLN	GLN	THR	THR					SER	PRO	PRO
183	SER	SER		LYS		LYS		LYS	SER	SER	LYS	LYS							LYS	ALA	ALA
184	ALA	THR		ALA		SER		ALA	ALA	ALA	SER	SER							ALA	THR	THR
185	GLN	GLN		GLN		ASN		GLN	GLN	GLN	ASN	ASN							ASP	ALA	ALA
186	TYR	TYR		TYR		TYR		TYR	TYR	TYR	TYR	TYR							TYR	TRP	TRP
187	ASN	ASN		ASN		ASN		ASN	ASN	ASN	ASN	ASN							GLU	ASN	ASN
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188	SER	SER		SER		SER		SER	SER	SER	SER	SER							LYS	LYS	LYS
189	HIS	HIS		HIS		HIS		HIS	HIS	HIS	HIS	HIS					TYR		HIS	GLY	GLY
190	SER	LYS		SER		ASN		SER	SER	SER	ASN	ASN					SER		LYS	SER	SER
191	VAL	GLU		---		GLU		VAL	VAL	VAL	GLU	GLN					THR		VAL	SER	SER
192	TYR	TYR		TYR		TYR		TYR	TYR	TYR	TYR	TYR			TYR		MET		TYR	TYR	TYR
193	THR	THR		THR		THR		THR	THR	THR	THR	THR			THR		THR		ALA	THR	THR
194	CYS	CYS		CYS		CYS		CYS	CYS	CYS	CYS	CYS			CYS		CYS		CYS	CYS	CYS
195	GLU	LYS		GLN		GLN		GLU	GLU	GLU	GLN	GLN			GLN		GLU		GLU	SER	SER
196	VAL	VAL		VAL		VAL		VAL	VAL	VAL	VAL				VAL		VAL		VAL	VAL	VAL
197	VAL	THR		HIS		ALA		VAL	VAL	VAL	ALA				ALA		---		---	---	---
198	---	---		---		---		---	---	---	---				---		HIS		HIS	HIS	HIS
199	GLN	GLN		ASN		GLN		HIS	GLN	GLN	GLN				GLN		PRO		GLN	GLY	GLY
200	GLY	GLY		SER		GLY		ASN	GLY	GLY	GLY				GLY		THR		GLY	SER	SER
201	SER	THR		ALA		ALA		SER	SER	SER	ALA				ASP		LEU		LEU	LEU	LEU
202	ALA	THR		ARG		GLY		GLY	ALA	ALA	GLY				GLY		THR		SER	SER	SER
203	SER	SER		SER		SER		SER	SER	SER	SER	SER			ALA		PRO		SER	SER	SER
204	PRO	---		---		---		ALA	LEU	PRO	---	---			---		ALA		PRO	PRO	PRO
205	ILE	VAL		ILE		VAL		ILE	ILE	ILE	VAL	VAL			GLN		LEU		VAL	LEU	LEU
206	VAL	VAL		VAL		VAL		VAL	VAL	VAL	VAL	VAL					ALA		THR	LEU	LEU
206A	---	---		---		---		---	---	---	---	---			---		---		---	---	---
207	GLN	GLN		GLX		GLN		GLN	GLN	GLN	GLN	GLN			ASN		LYS		LYS	LYS	LYS
208	SER	SER		SER		SER		SER	SER	SER	SER	SER			GLY		SER			THR	THR
209	PHE	PHE		PHE		PHE		PHE	PHE	PHE	PHE	PHE			PHE		PHE			ILE	ILE
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210	ASN	ASN		ASN		SER		ASN	ASN	ASN	SER	SER	SER				GLN			SER	SER
211	ARG	ARG		ARG		ARG		ARG	ARG	ARG	ARG	ARG	ARG		ARG		THR			SER	SER
212	GLY	GLY		GLY		LYS		GLY	GLY	GLY	LYS	LYS	LYS	LYS	LYS		SER			THR	THR
213	ASP	ASP		ASP		ASN		ASP	ASP	ASP	ASN	ASN	SER	SER	ASN		GLU			ALA	ALA
214	CYS	CYS		CYS		CYS		CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS		CYS			CYS	CYS
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KAPPA LIGHT CONSTANT CHAINS (cont'd)

	64 HORNED SHARK 1122 'CL	65 1XIg31 'CL #	# OF SEQUENCES	# OF AMINO ACIDS	OCCURRENCES OF MOST COMMON AMINO ACID	VARIABILITY
107A	---	---				
108	---	ARG	37	6	20(ARG)	11.
109	SER	ASN	60	7	29(ALA)	14.
109A	GLU	---	8	2	4(+)	
110	ASP	ASP	58	5	25(ASP),21(ASP)	12.,14.
111	ARG	ALA	57	5	34(ALA)	8.4
112	LYS	LYS	58	4	52(ALA)	4.5
113	**PRO**	**PRO**	59	2	58(PRO)	2.
114	SER	ALA	59	4	37(THR)	6.4
115	**VAL**	**VAL**	59	1	59(VAL)	1.
116	LEU	PHE	59	3	24(LEU)	7.4
117	LEU	ILE	59	2	46(ILE)	2.6
118	LEU	PHE	59	3	55(PHE)	3.2
119	**PRO**	LYS	59	3	57(PRO)	3.1
120	**PRO**	**PRO**	59	1	59(PRO)	1.
121	SER	SER	59	2	54(SER)	2.2
122	SER	ASP	60	9	24(SER)	22.
123	GLU	GLU	60	3,4	44(GLU),39(GLU)	4.1,6.2
124	GLU	GLN	60	4	45(GLN),40(GLN)	5.3,6.
124A	---	---				
125	ILE	VAL	60	4	51(LEU)	4.7
126	**ASP**	LYS	60	5	23(THR)	13.
127	SER	GLU	60	5	28(+)	11.
128	GLY	GLY	59	2,3	55(GLY)	2.1,3.2
129	TRP	ASN	60	7	29(THR)	14.
130	ALA	PRO	60	3	48(ALA)	3.7
131	THR	THR	60	2	33(SER)	3.6
132	LEU	ALA	58	5	34(VAL)	8.5
133	SER	**VAL**	59	2	56(VAL)	2.1
134	**CYS**	**CYS**	61	1	61(CYS)	1.
135	LEU	LEU	60	4	20(+)	12.
136	VAL	ILE	62	5	22(LEU)	14.
137	SER	ASN	61	3	56(ASN),55(ASN)	3.3
138	ARG	ASN	61	6	33(ASN),31(ASN)	11.,12.
139	PHE	PHE	63	2	50(PHE)	2.5
140	LYS	PHE	62	4	42(TYR)	5.9
141	**PRO**	**PRO**	63	1	63(PRO)	1.
142	GLY	ARG	64	6	22(ARG)	17.
143	PHE	ASP	64	5,6	36(ASP),33(ASP)	8.9,12.
144	VAL	LEU	51	4	35(ILE)	5.8
145	ARG	THR	64	6	23(THR)	17.
146	**VAL**	**VAL**	64	2	63(VAL)	2.
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147	LEU	THR	62	4	26(LYS)	9.5
148	**TRP**	**TRP**	62	2	62(TRP)	1.
149	ARG	LYS	62	4	51(LYS)	4.9
150	VAL	VAL	61	2	35(VAL)	3.5
151	**ASP**	**ASP**	61	2	60(ASP),58(ASP)	2.,2.1
152	ASP	SER	60	4	42(GLY)	5.7
153	LYS	GLN	58	7	19(SER)	21.
154	GLU	ASP	59	6,7	28(GLU),26(GLU)	13.,16.
155	THR	VAL	59	5,6	27(GLN),26(GLN)	11.,14.
156	ASP	SER	57	5,6	24(GLN),22(GLN)	12.,16.
157	SER	SER	59	5	20(ASN),14(SER)	15.,21.
158	GLY	SER	60	4	43(GLY)	5.6
159	VAL	ASP	60	4	28(VAL)	8.6
160	THR	VAL	58	6	24(LEU)	14.
161	THR	LYS	55	5,6	29(ASN),25(ASN)	9.5,13.
162	GLY	THR	55	3	51(SER)	3.2
163	THR	SER	54	6,7	23(VAL)	14.,16.
164	VAL	ASP	55	3	51(THR)	3.2
165	SER	PHE	55	6,7	21(ASP),19(PRO)	16.,20.
166	THR	MET	55	4,5	49(GLN),45(GLN)	4.5,6.1
167	ASP	GLN	57	4	38(ASP),34(ASP)	6.,6.7
168	SER	GLU	56	4	44(SER)	5.1
169	ASP	SER	59	5	36(LYS)	8.2
170	GLN	ASP	56	2,3	53(ASP),52(ASP)	2.1,3.2
171	---	SER	52	3	34(SER)	4.6
172	SER	**THR**	56	2	55(THR)	2.
173	**TYR**	**TYR**	56	1	56(TYR)	1.
174	SER	SER	55	2	43(SER)	2.6
175	LEU	GLN	56	3	33(LEU)	5.1
176	**SER**	**SER**	56	1	56(SER)	1.
177	**SER**	**SER**	56	1	56(SER)	1.
178	TYR	MET	56	3	52(THR)	3.2
179	**LEU**	**LEU**	55	1	55(LEU)	1.
180	ARG	THR	55	3	40(THR)	4.1
181	VAL	**LEU**	55	2	52(LEU)	2.1
182	PRO	THR	54	6	34(THR)	9.5
183	ALA	LYS	52	3	40(LYS)	3.9
184	THR	ASP	54	5,6	30(ALA)	9.,11.
185	ALA	LYS	54	6	22(ASP)	15.
186	TRP	TRP	53	2	49(TYR)	2.2
187	ASN	ASP	53	4	32(GLU),30(GLU)	6.6,7.1
188	LYS	LYS	53	3	24(SER)	6.6
189	GLY	ALA	53	4	48(HIS)	4.4
190	SER	ASP	53	4	25(ASN),23(ASN)	8.5,9.2
191	SER	LYS	52	4	17(VAL)	21.
192	TYR	PHE	54	3	48(TYR)	3.4
193	THR	GLU	54	4	39(THR)	5.7
194	**CYS**	**CYS**	54	1	54(CYS)	1.
195	SER	LEU	56	5	40(GLU),38(GLU)	7.,7.4
196	VAL	VAL	55	5	44(VAL)	2.5
197	ASP	LYS	55	6	26(THR)	13.
198	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
199	GLY	LYS	55	6	25(LYS)	13.
200	SER	THR	55	4	26(THR)	8.5
201	LEU	ALA	53	5	30(SER)	8.8
202	SER	GLN	53	6	18(SER)	18.
203	SER	LEU	54	4	31(SER)	4.2
204	PRO	THR	46	4	41(PRO)	4.5
205	LEU	GLN	54	4	29(VAL)	7.7
206	LEU	SER	53	5	37(VAL)	7.2
206A	---	---	[illegible]	[illegible]	1(TRP)	
207	LYS	PHE	56	4,5	39(LYS)	5.7,7.2
208	THR	SER	55	4	50(SER)	4.4
209	ILE	LYS	54	3	50(PHE)	3.2
210	SER	---	53	3	44(ASN)	3.6
211	SER	---	46	4	49(ARG)	4.5
212	THR	SER	57	5	24(ASN)	12.
213	ALA	GLN	57	9	35(GLU)	9.8
214	**CYS**	**CYS**	57	2	57(CYS)	1.
215	SER	SER	5	2	4(SER)	2.5
216	ASP	---	4	2	3(ASP)	2.7

Express Mail No EV 531 711 295 US
Date Mailed: 9/7/2004
Serial No. 10/020,354
Inventor Dall'Acqua et al.
First Class Mail ☐
Filed December 12, 2001
OK
For MOLECULES WITH EXTENDED HALF-LIVES, COMPOSITIONS AND USES THEREOF

1. Petition for Extension of Time Under 37 CFR Section 1.136(a) (in duplicate);
2. Fee Transmittal Sheet (in duplicate);
3. Amendment Under 37 C.F.R. Section 1.111;
4. A copy of the Information Disclosure Statement;
5. A copy of the Revised PTO-1449 Form;
6. References AA-CZ; and
7. Exhibit A, SYNAGIS® product information from the 2001 and 2004 Physicians' Desk References

File no.: 10271-027

Sender: AMI/JJC

Express Mail No EV 531 711 295 US
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2001

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ISBN: 1-56363-330-2

Total Quantity of Immunoglobulin	Volume	Concentration
1000 mg ± 200 mg	20 ml	50 ± 10 mg/ml
2500 mg ± 500 mg	50 ml	50 ± 10 mg/ml

...to sensitized to immune globu...
...may be related to the rate of infu...
...to the infusion rates as out...
...AND ADMINISTRATION." If ana...
...pressure occurs, *discontinue*...
...with diphenhydramine and ad...

...possible, clinical experience with ...tions suggests that the major ...related to volume overload.

...MINISTRATION

...total dosage per infusion is ...according to the following

...ge and

...Remove the tab portion of ...rubber stopper with 70% alcohol ...SHAKE VIAL; AVOID FOAMING. ...should be inspected visually for ...ration prior to administration ...permit. Infuse the solution ...particulate matter and not tur...

...in within 6 hours after enter...complete within 12 hours of en...should be taken preinfusion, mid...well as before any rate increase. ...tered through an intravenous ...that contains an in-line fil...constant infusion pump (i.e., IVAC ...in-line filter (0.2μ) is also ...CytoGam® before infusion is not

...tered through a separate in...possible, CytoGam® may be ...ing line if that line contains ...USP, or one of the follow...(without NaCl added): 2.5% ...in water, 10% dextrose in ...If a pre-existing line must be ...not be diluted more than 1:2 ...solutions. Admixtures of Cy...have not been evaluated. ...intravenously at 15 mg Ig per kg ...adverse reactions occur after 30 ...increased to 30 mg Ig/kg/hr; if no ...subsequent 30 minutes, then ...to 60 mg Ig/kg/hr (volume not ...EXCEED THIS RATE OF ...patient should be monitored ...rate change.

...at 15 mg Ig/kg/hr for 15 ...occur, increase to 30 mg ...then increase to a maximum ...not to exceed 75 ml/hour). ...RATE OF ADMINISTRATION. ...closely during each rate

...with caution in patients with ...and in patients judged to be ...renal insufficiency (includ...with diabetes mellitus, age ...paraproteinemia, sepsis ...nephrotoxic drugs). In these ...to assure that patients are ...to CytoGam® infusion. While ...have occurred in patients ...Ig/kg or greater, no prospec...to identify a maximum safe ...of infusion in patients deter...of acute renal failure. In the ...recommended doses should not ...infusion and infusion rate se...practicable. The product ...of 150 mg Ig/kg/hr or less.

...are: flushing, chills, muscle ..., vomiting, wheezing, drop ...reactions have been infu...patient develops a minor side ef...flushing), slow the rate or tem...If anaphylaxis or drop in ...infusion and use antidote ...adrenalin.

...of hepatitis viruses or other in...person to another, sterile dispos...should be used. The syringes and

...Immune Globulin Intrave...in two single-dose vial forms:

...between 2° C and 8° C (35.6° F ...within 6 hours after entering the

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For additional information concerning Cytomegalovirus Immune Globulin Intravenous (Human) contact:

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35 West Watkins Mill Road
Gaithersburg, MD 20878, USA
1-800-949-3789

Manufactured by:

MASSACHUSETTS PUBLIC HEALTH BIOLOGIC LABORATORIES

Boston, Massachusetts 02130, USA

U.S. Govt. License No. 64

Marketed by:

MedImmune Inc.

35 W. Watkins Mill Road
Gaithersburg, MD 20878

Revised April 2000

Shown in Product Identification Guide, page 323

SYNAGIS®
(palivizumab)
for Intramuscular Administration

B

DESCRIPTION

Synagis® (palivizumab) is a humanized monoclonal antibody (IgG1κ) produced by recombinant DNA technology, directed to an epitope in the A antigenic site of the F protein of respiratory syncytial virus (RSV). Palivizumab is a composite of human (95%) and murine (5%) antibody sequences. The human heavy chain sequence was derived from the constant domains of human IgG1 and the variable framework regions of the V_H genes Cor (1) and Cess (2). The human light chain sequence was derived from the constant domain of Cκ and the variable framework regions of the V_L gene K104 with Jκ -4 (3). The murine sequences were derived from a murine monoclonal antibody, Mab 1129 (4), in a process which involved the grafting of the murine complementarity determining regions into the human antibody frameworks. Synagis® is composed of two heavy chains and two light chains and has a molecular weight of approximately 148,000 Daltons.

Synagis® is supplied as a sterile lyophilized product for reconstitution with sterile water for injection. Reconstituted Synagis® is to be administered by intramuscular injection only. Upon reconstitution, Synagis® contains the following excipients: 47 mM histidine, 3.0 mM glycine and 5.6% mannitol and the active ingredient, palivizumab, at a concentration of 100 milligrams per vial. The reconstituted solution should appear clear or slightly opal[illegible]

CLINICAL PHARMACOLOGY

Mechanism of Action: Synagis® ex[illegible]eutralizing and fusion-inhibitory activity against RSV. These activities inhibit RSV replication in laboratory experiments. Although resistant RSV strains may be isolated in laboratory studies, a panel of 57 clinical RSV isolates were all neutralized by Synagis® (5). Synagis® serum concentrations of ≥ 40 μg/ml have been shown to reduce pulmonary RSV replication in the cotton rat model of RSV infection by 100-fold (5). The *in vivo* neutralizing activity of the active ingredient in Synagis® was assessed in a randomized, placebo-controlled study of 35 pediatric patients tracheally intubated because of RSV disease. In these patients, palivizumab significantly reduced the quantity of RSV in the lower respiratory tract compared to control patients (6).

Pharmacokinetics: In studies in adult volunteers Synagis® had a pharmacokinetic profile similar to a human IgG1 antibody in regard to the volume of distribution and the half-life (mean 18 days). In pediatric patients less than 24 months of age, the mean half-life of Synagis® was 20 days and monthly intramuscular doses of 15 mg/kg achieved mean ±SD 30 day trough serum drug concentrations of 37 ±21 μg/mL after the first injection, 57 ±41 μg/mL after the second injection, 68 ±51 μg/mL after the third injection and 72 ±50 μg/mL after the fourth injection (7). In pediatric patients given Synagis® for a second season, the mean ±SD serum concentrations following the first and fourth injections were 61 ±17 μg/mL and 86 ±31 μg/mL, respectively.

CLINICAL STUDIES

The safety and efficacy of Synagis® were assessed in a randomized, double-blind, placebo-controlled trial (IMpact-RSV Trial) of RSV disease prophylaxis among high-risk pediatric patients (7). This trial, conducted at 139 centers in the United States, Canada and the United Kingdom, studied patients ≤ 24 months of age with bronchopulmonary dysplasia (BPD) and patients with premature birth (≤ 35 weeks gestation) who were ≤ 6 months of age at study entry. Patients with uncorrected congenital heart disease were excluded from enrollment. In this trial, 500 patients were randomized to receive five monthly placebo injections and 1,002 patients were randomized to receive five monthly injections of 15 mg/kg of Synagis®. Subjects were randomized into the study from November 15 to December 13, 1996, and were followed for safety and efficacy for 150 days. Ninety-nine percent of all subjects completed the study and 93% received all five injections. The primary endpoint was the incidence of RSV hospitalization.

RSV hospitalizations occurred among 53 of 500 (10.6%) patients in the placebo group and 48 of 1002 (4.8%) patients in the Synagis® group, a 55% reduction ($p<0.001$). The reduction of RSV hospitalization was observed both in patients enrolled with a diagnosis of BPD (34/266 [12.8%] placebo vs 39/496 [7.9%] Synagis®) and patients enrolled with a diagnosis of prematurity without BPD (19/234 [8.1%] placebo vs 9/506 [1.8%] Synagis®). The reduction of RSV hospitalization was observed throughout the course of the RSV season. Among secondary endpoints, the incidence of ICU admission during hospitalization for RSV infection was lower among subjects receiving Synagis® (1.3%) than among those receiving placebo (3.0%), but there was no difference in the mean duration of ICU care between the two groups for patients requiring ICU care. Overall, the data do not suggest that RSV illness was less severe among patients who received Synagis® and who required hospitalization due to RSV infection than among placebo patients who required hospitalization due to RSV infection. Synagis® did not alter the incidence and mean duration of hospitalization for non-RSV respiratory illness or the incidence of otitis media.

Continued on next page

Synagis—Cont.

INDICATIONS AND USAGE

Synagis® is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk of RSV disease. Safety and efficacy were established in infants with bronchopulmonary dysplasia (BPD) and infants with a history of prematurity (≤ 35 weeks gestational age). (See *Clinical Studies* section)

CONTRAINDICATIONS

Synagis® should not be used in pediatric patients with a history of a severe prior reaction to Synagis® or other components of this product.

WARNINGS

Anaphylactoid reactions following the administration of Synagis® have not been observed but can occur following the administration of proteins. If anaphylaxis or severe allergic reaction occurs, administer epinephrine (1:1000) and provide supportive care as required.

PRECAUTIONS

General: Synagis® is for intramuscular use only. As with any intramuscular injection, Synagis® should be given with caution to patients with thrombocytopenia or any coagulation disorder.

The safety and efficacy of Synagis® have not been demonstrated for treatment of established RSV disease.

The single-use vial of Synagis® does not contain a preservative. Injections should be given within 6 hours after reconstitution.

Immunogenicity: In the IMpact-RSV trial, the incidence of anti-humanized antibody following the fourth injection was 1.1% in the placebo group and 0.7% in the Synagis® group. In pediatric patients receiving Synagis® for a second season, one of fifty-six patients had transient, low titer reactivity. This reactivity was not associated with adverse events or alteration in Synagis® serum concentrations.

Drug Interactions: No formal drug-drug interaction studies were conducted. In the IMpact-RSV trial, the proportions of patients in the placebo and Synagis® groups who received routine childhood vaccines, influenza vaccine, bronchodilators or corticosteroids were similar and no incremental increase in adverse reactions was observed among patients receiving these agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis, mutagenesis and reproductive toxicity studies have not performed.

Pregnancy: Pregnancy Category C: Synagis® is not indicated for adult usage and animal reproduction studies have not been conducted. It is also not known whether Synagis® can cause fetal harm when administered to a pregnant woman or could affect reproductive capacity.

ADVERSE REACTIONS

In the combined pediatric prophylaxis studies of pediatric patients with BPD or prematurity involving 520 subjects receiving placebo and 1168 subjects receiving Synagis®, the proportions of subjects in the placebo and Synagis® groups who experienced any adverse event or any serious adverse event were similar.

Most of the safety information was derived from the IMpact-RSV trial. In this study, Synagis® (palivizumab) was discontinued in five patients: two because of vomiting and diarrhea, one because of erythema and moderate induration at the site of the fourth injection, and two because of pre-existing medical conditions which required management (one with congenital anemia and one with pulmonary venous stenosis requiring cardiac surgery). Deaths in study patients occurred in five of 500 placebo recipients and four of 1002 Synagis® recipients. Sudden infant death syndrome was responsible for two of these deaths in the placebo group and one death in the Synagis® group. Adverse events which occurred in more than 1% of patients receiving Synagis® in the IMpact-RSV study for which the incidence in the Synagis® group was 1% greater than in the placebo group are shown in Table 1.

Table 1. Adverse Events Occurring in IMpact-RSV Study at Greater Frequency in the Synagis® Group

% of patients with:	Placebo n = 500	Synagis® n = 1002
upper respiratory infection	49.0%	52.6%
otitis media	40.0%	41.9%
rhinitis	23.4%	28.7%
rash	22.4%	25.6%
pain	6.8%	8.5%
hernia	5.0%	6.3%
SGOT increased	3.8%	4.9%
pharyngitis	1.4%	2.6%

Other adverse events reported in more than 1% of the Synagis® group included: fever, cough, wheeze, bronchiolitis, pneumonia, bronchitis, asthma, croup, dyspnea, sinusitis, apnea, failure to thrive, nervousness, diarrhea, vomiting, and gastroenteritis, SGPT increased, liver function abnormality, study drug injections site reaction, conjunctivitis, viral infection, oral monilia, fungal dermatitis, eczema, seborrhea, anemia and flu syndrome. The incidence of these adverse events was similar between the Synagis® and placebo groups.

OVERDOSAGE

No data from clinical studies are available on overdosage. No toxicity was observed in rabbits administered a single intramuscular or subcutaneous injection of Synagis® at a dose of 50 mg/kg. No data are available from human subjects who have received more than 5 monthly Synagis® doses during a single RSV season.

DOSAGE AND ADMINISTRATION

The recommended dose of Synagis® is 15 mg/kg of body weight. Patients, including those who develop an RSV infection, should receive monthly doses throughout the RSV season. The first dose should be administered prior to commencement of the RSV season. In the northern hemisphere, the RSV season typically commences in November and lasts through April, but it may begin earlier or persist later in certain communities.

Synagis® should be administered in a dose of 15 mg/kg intramuscularly using aseptic technique, preferably in the anterolateral aspect of the thigh. The gluteal muscle should not be used routinely as an injection site because of the risk of damage to the sciatic nerve. The dose per month = [patient weight (kg) × 15 mg/kg ÷ 100 mg/mL of Synagis®]. Injection volumes over 1 mL should be given as a divided dose.

Preparation for Administration

- To reconstitute, remove the tab portion of the vial cap and clean the rubber stopper with 70% ethanol or equivalent.
- Both the 50 mg and 100 mg vials contain an overfill to allow the withdrawal of 50 milligrams or 100 milligrams respectively when reconstituted following the directions described below.
- Slowly add 0.6 mL of sterile water for injection to the 50 mg vial or add 1.0 mL of sterile water for injection to the 100 mg vial. The vial should be gently swirled for 30 seconds to avoid foaming. DO NOT SHAKE VIAL.
- Reconstituted Synagis® should stand at room temperature for a minimum of 20 minutes until the solution clarifies.
- Reconstituted Synagis® does not contain a preservative and should be administered within 6 hours of reconstitution

To prevent the transmission of hepatitis viruses or other infectious agents from one person to another, sterile disposable syringes and needles should be used. Do not reuse syringes and needles.

HOW SUPPLIED

Synagis® is supplied in single use vials as lyophilized powder to deliver either 50 milligrams or 100 milligrams when reconstituted with sterile water for injection.

50 mg vial NDC 60574-4112-1

Upon reconstitution the 50 mg vial contains 50 milligrams Synagis® in 0.5 mL.

100 mg vial NDC 60574-4111-1

Upon reconstitution the 100 mg vial contains 100 milligrams Synagis® in 1.0 mL.

Upon receipt and until reconstitution for use, Synagis® should be stored between 2 and 8°C (35.6° and 46.4°F) in its original container. Do not freeze. Do not use beyond the expiration date.

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3. Bentley D, and Rabbitts T. Human immunoglobulin variable region genes – DNA sequences of two V_k genes and a pseudogene. Nature 1980;288:730–733.
4. Beeler JA and Van Wyke Coelingh K. Neutralization epitopes of the F Protein of Respiratory Syncytial Virus: Effect of mutation upon fusion function. J. Virology 1989;63:2941–2950
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7. The IMpact RSV Study Group. Palivizumab, a Humanized Respiratory Syncytial Virus Monoclonal Antibody, Reduces Hospitalization From Respiratory Syncytial Virus Infection in High-risk Infants. *Pediatrics in press.*

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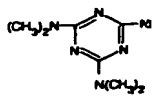
Manufactured by:
MedImmune, Inc.
Gaithersburg, MD 20878
(1-877-633-4411)

Co-Marketed by:
Ross Products Division
Abbott Laboratories, Inc.
Columbus, Ohio 43215-1724
Rev. date: December 2, 1999
Shown in Product Identificati

DESCRIPTION

HEXALEN (altretamine), is a synth
plastic s-triazine derivative. HEXAL
mg of altretamine for oral administr
include lactose, anhydrous and ca
tamine, known chemically as *N,N,*
ethyl-1,3,5-triazine-2,4,6-triamine, b
tural formula:



Its empirical formula is $C_9H_{18}N_6$ with
210.28. Altretamine is a white cryst
at 172° ± 1°C. Altretamine is practic
but is increasingly soluble at pH 3 a

CLINICAL PHARMACOLOGY

The precise mechanism by which HE
totoxic effect is unknown, although a
possibilities have been studied. Struc
semblies the alkylating agent triethy
vitro tests for alkylating activity of I
tabolites have been negative. HEXA
strated to be efficacious for certain ov
to classical alkylating agents. Metab
a requirement for cytotoxicity. Synt
ethylmelamines, and products of alt
in vitro and *in vivo*, can form covale
macromolecules including DNA, but
reactions to antitumor activity is unl
HEXALEN is well-absorbed followir
in humans, but undergoes rapid and
tion in the liver, producing variation
levels. The principal metabolites are
and tetramethylmelamine.
Pharmacokinetic studies were perfor
ber of patients and should be conside
oral administration of HEXALEN to
vanced ovarian cancer in doses of
plasma levels (as measured by gas-cl
were reached between 0.5 and 3 hou
20.8 mg/l. Half-life of the β-phase
from 4.7 to 10.2 hours. Altretamine
binding to plasma proteins. The fr
tamine, pentamethylmelamine and
are 6%, 25% and 50%, respectively.

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2004

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	Total Quantity of Immunoglobulin	Volume	Concentration
	1000 mg ± 200 mg	20 ml	50 ± 10 mg/ml
	2500 mg ± 500 mg	50 ml	50 ± 10 mg/ml

tal signs should be taken preinfusion, mid-ion as well as before any rate increase. d be administered through an intravenous inistration set that contains an in-line fil- and a constant infusion pump (i.e., IVAC). A smaller in-line filter (0.2μ) is also tion of CytoGam® before infusion is not CytoGam® should be administered through avenous line. If this is not possible, be "piggybacked" into a pre-existing line if either Sodium Chloride, Injection, USP, or ing dextrose solutions (with or without dextrose in water, 5% dextrose in water, water, 20% dextrose in water. If a pre- be used, the CytoGam® should not be di- 1:9 with any of the above-named solutions. toGam® with any other solutions have not

dminister intravenously at 15 mg Ig per kg hour. If no adverse reactions occur after 30 may be increased to 30 mg Ig/kg/hr; if no occur after a subsequent 30 minutes, then be increased to 60 mg Ig/kg/hr (volume not hour). DO NOT EXCEED THIS RATE OF TION. The patient should be monitored and after each rate change.

ies. Administer at 15 mg Ig/kg/hr for 15 adverse reactions occur, increase to 30 mg minutes and then increase to a maximum Ig/kg/hr (volume not to exceed 75 ml/hour). ED THIS RATE OF ADMINISTRATION. uld be monitored closely during each rate

Cytomegalovirus Immune Globulin Intrave- (CMV-IGIV), should be used with caution in pre-existing renal insufficiency and in pa- s at increased risk of developing renal in- ding, but not limited to those with diabetes ater than 65, volume depletion, paraprote- and patients receiving known nephrotoxic s e especially, it is important to assure are not volume depleted prior to CytoGam® most cases of renal insufficiency have patients receiving total doses of 400 mg Ig/kg or pective data are presently available to iden- a safe dose, concentration or rate of infusion mined to be at increased risk of acute renal e of prospective data, recommended be exceeded and the concentration and in- ted should be the minimum practicable. uld be infused at a rate of 180 mg Ig/kg/hr

se reactions are: flushing, chills, muscle , fever, nausea, vomiting, wheezing, drop ure. Minor adverse reactions have been infu- —if the patient develops a minor side ef- , back pain, flushing), slow the rate or tem- the infusion. If anaphylaxis or drop in occurs, discontinue infusion and use antidote hydramine and adrenalin. transmission of hepatitis viruses or other in- from one person to another, sterile dispos- needles should be used. The syringes and not be reused.

egalovirus Immune Globulin Intrave- is supplied in two single-dose vial forms:

uld be stored between 2° C and 8° C (35.6° F used within 6 hours after entering the

McIver J, Leszczynski J, et al. A pilot trial megalovirus immune globulin in renal trans- Transplantation 38:553–557, 1984. 2. Ho- ME, Lippin A, et al. Inactivation of viruses derivatives. Transfusion; 25:516–522, 1985. Werner BG, and Heinze-Lacey BH, et al. virus immune globulin to prevent cyto- in renal transplant recipients. NEJM 1987. 4. Snydman DR, Werner BG, Dou- Cytomegalovirus Immune Globulin pro- transplantation. A randomized, double- controlled trial. Ann Int Med 119:984–991, ME, Snydman DR, Ruthazer R. et al. Cy- Immune Globulin (CMVIG) prophylaxis is increased survival after orthotopic liver Clin Transplantation, 11:432–437, 1997. 6. Werner BG, Tilney NL, et al. A final analysis megalovirus disease prevention in renal nts with a cytomegalovirus immune glob- a of randomized and open-label trials. ed 23:1357–1360, 1991. 7. Snydman DR, gherty NN, et al. A further analysis of the lovirus Immune Globulin in orthotopic liver nts at risk for primary infection. Transplant Proceed 26, suppl 1:23–27, 1994. 8. Merigan TC, Renlund DG, Keay S et al. A controlled trial of ganciclovir to prevent cytomegalovirus disease after heart transplantation. NEJM 326:1182–1186, 1992. 9. Ham JM, Shelden SR, Godkin RR, et al. Cytomegalovirus prophylaxis with ganciclovir, acyclovir and CMV hyperimmune globulin in liver transplant patients receiving OKT3 induction. Transplant Proc; 27 (5 Suppl 1):31–33, 1995. 10. Snydman DR. Combined CMV-IGIV and ganciclovir prophylaxis in CMV seronegative transplant recipients from CMV seropositive donors. Report on file, MedImmune, Inc. 11. Martin M. CMV prophylaxis with combination ganciclovir and CMV hyperimmune globulin followed by high-dose acyclovir in solid organ transplant recipients. Report on file, MedImmune, Inc. 12. Valantine H and Luikart H. Impact of CMV hyperimmune globulin on outcome after cardiothoracic transplantation: A comparative study of combined prophylaxis with CMVIG plus ganciclovir vs. ganciclovir alone. Report on file, MedImmune, Inc. 13. Bossell, et al. Safety of therapeutic immune globulin preparations with respect to transmission of human T-lymphotropic virus type III/lymphadenopathy-associated virus infection. MMWR vol. 35:231–233, April 11, 1996. 14. Wells MA, Wittek AE, Epstein JS, et al. Inactivation and partition of human T-cell lymphotropic virus, type III, during ethanol fractionation of plasma. Transfusion 26:210–213, 1986. 15. McIver J, Grady G. Immunoglobulin preparations. In: Churchill WH and Kurtz SR, (ed): Transfusion Medicine. Boston: Blackwell; 1988. 16. Schneider L, Geha R. Outbreak of Hepatitis C associated with intravenous immunoglobulin administration—United States, October 1993–June 1994. MMWR vol. 43:505–509, July 22, 1994. 17. Edwards CA, Piet MPJ, Chin S, et al. Tri(nButyl) phosphate detergent treatment of licensed therapeutic and experimental blood derivatives. Vox Sang 52:53–59, 1987. 18. Cayco AV, Perazella MA, Hayslett JP. Renal insufficiency after intravenous immune globulin therapy: A report of two cases and an analysis of the literature. J Am Soc Nephrology; 8: 1788–1793, 1997. 19. Cantu TG, Hoehn-Saric EW, Burgess KM et al. Acute renal failure associated with immunoglobulin therapy. Am J Kidney Dis; 25: 228–234, 1995. 20. Hansen-Schmidt S., Silomon J, Keller F. Osmotic nephrosis due to high-dose immunoglobulin therapy containing sucrose (but not with glycine) in a patient with immunoglobulin A nephritis. Am. J. Kidney Dis.; 28: 451–453, 1996. 21. Sekul E, Culper E, Dalaks M. Aseptic meningitis associated with high-dose intravenous immunoglobulin therapy; Frequency and risk factors. Ann Int Med; 121:259–262, 1994. 22. Kato E, Shindo S, Eto Y, et al. Administration of immune globulin associated with aseptic meningitis. JAMA; 259:3269–3270, 1988. 23. Casteels Van Daele M, Wijndaele L, Hunnick K, et al. Intravenous immunoglobulin and acute aseptic meningitis. NEJM; 323:614–615, 1990. 24. Scribner C, Kapit R, Philips E, et al. Aseptic meningitis and intravenous immunoglobulin therapy. Ann Intern Med; 121:305–306, 1994.

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Shown in Product Identification Guide, page 324

SYNAGIS®

(palivizumab) ℞

for Intramuscular Administration

DESCRIPTION

Synagis® (palivizumab) is a humanized monoclonal antibody (IgG1κ) produced by recombinant DNA technology, directed to an epitope in the A antigenic site of the F protein of respiratory syncytial virus (RSV). Palivizumab is a composite of human (95%) and murine (5%) antibody sequences. The human heavy chain sequence was derived from the constant domains of human IgG1 and the variable framework regions of the V_H genes Cor (1) and Cess (2). The human light chain sequence was derived from the constant domain of Cκ and the variable framework regions of the V_L gene K104 with Jκ -4 (3). The murine sequences were derived from a murine monoclonal antibody, Mab 1129 (4), in a process which involved the grafting of the murine complementarity determining regions into the human antibody frameworks. Synagis® (palivizumab) is composed of two heavy chains and two light chains and has a molecular weight of approximately 148,000 Daltons.

Synagis® (palivizumab) is supplied as a sterile lyophilized product for reconstitution with sterile water for injection. Reconstituted Synagis® (palivizumab) is to be administered by intramuscular injection only. Upon reconstitution, Synagis® (palivizumab) contains the following excipients: 47 mM histidine, 3.0 mM glycine and 5.6% mannitol and the active ingredient, palivizumab, at a concentration of 100 milligrams per ml solution. The reconstituted solution should appear clear or slightly opalescent.

CLINICAL PHARMACOLOGY

Mechanism of Action: Synagis® (palivizumab) exhibits neutralizing and fusion-inhibitory activity against RSV. These activities inhibit RSV replication in laboratory experiments. Although resistant RSV strains may be isolated in laboratory studies, a panel of 57 clinical RSV isolates were all neutralized by Synagis® (palivizumab) (5). Synagis® (palivizumab) serum concentrations of ≥ 40 μg/ml have been shown to reduce pulmonary RSV replication in the cotton rat model of RSV infection by 100-fold (5). The *in vivo* neutralizing activity of the active ingredient in Synagis® (palivizumab) was assessed in a randomized, placebo-controlled study of 35 pediatric patients tracheally intubated because of RSV disease. In these patients, palivizumab significantly reduced the quantity of RSV in the lower respiratory tract compared to control patients (6).

Pharmacokinetics: In studies in adult volunteers Synagis® (palivizumab) had a pharmacokinetic profile similar to a human IgG1 antibody in regard to the volume of distribution and the half-life (mean 18 days). In pediatric patients less than 24 months of age, the mean half-life of Synagis® (palivizumab) was 20 days and monthly intramuscular doses of 15 mg/kg achieved mean ±SD 30 day trough serum drug concentrations of 37 ±21 μg/mL after the first injection, 57 ±41 μg/mL after the second injection, 68 ±51 μg/mL after the third injection and 72 ±50 μg/mL after the fourth injection (7). In pediatric patients given Synagis® (palivizumab) for a second season, the mean ±SD serum concentrations following the first and fourth injections were 61 ±17 μg/mL and 86 ±31 μg/mL, respectively.

CLINICAL STUDIES

The safety and efficacy of Synagis® (palivizumab) were assessed in a randomized, double-blind, placebo-controlled trial (IMpact-RSV Trial) of RSV disease prophylaxis among high-risk pediatric patients (7). This trial, conducted at 139 centers in the United States, Canada and the United Kingdom, studied patients ≤ 24 months of age with bronchopulmonary dysplasia (BPD) and patients with premature birth (≤ 35 weeks gestation) who were ≤ 6 months of age at study entry. Patients with uncorrected congenital heart disease were excluded from enrollment. In this trial, 500 patients were randomized to receive five monthly placebo injections and 1,002 patients were randomized to receive five monthly injections of 15 mg/kg of Synagis® (palivizumab). Subjects were randomized into the study from November 15 to December 13, 1998, and were followed for safety and efficacy for 150 days. Ninety-nine percent of all subjects completed the study and 93% received all five injections. The primary endpoint was the incidence of RSV hospitalization.

RSV hospitalizations occurred among 53 of 500 (10.6%) patients in the placebo group and 48 of 1002 (4.8%) patients in the Synagis® (palivizumab) group, a 55% reduction ($p<0.001$). The reduction of RSV hospitalization was observed both in patients enrolled with a diagnosis of BPD (34/266 [12.8%] placebo vs 39/496 [7.9%] Synagis® [palivizumab] and patients enrolled with a diagnosis of prematurity without BPD (19/234 [8.1%] placebo vs 9/506 [1.8%] Synagis® [palivizumab]). The reduction of RSV hospitalization was observed throughout the course of the RSV season.

Among secondary endpoints, the incidence of ICU admission during hospitalization for RSV infection was lower among subjects receiving Synagis® (palivizumab) (1.3%) than among those receiving placebo (3.0%), but there was no difference in the mean duration of ICU care between the two groups for patients requiring ICU care. Overall, the data do not suggest that RSV illness was less severe among patients who received Synagis® (palivizumab) and who required hospitalization due to RSV infection than among placebo patients who required hospitalization due to RSV infection. Synagis® (palivizumab) did not alter the incidence and mean duration of hospitalization for non-RSV respiratory illness or the incidence of otitis media.

INDICATIONS AND USAGE

Synagis® (palivizumab) is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk of RSV disease. Safety and efficacy were established in infants with bronchopulmonary dysplasia (BPD) and infants with a history of prematurity (≤ 35 weeks gestational age). (See *Clinical Studies* section)

CONTRAINDICATIONS

Synagis® (palivizumab) should not be used in pediatric patients with a history of a severe prior reaction to Synagis® (palivizumab) or other components of this product.

WARNINGS

Very rare cases of anaphylaxis (<1 case per 100,000 patients) have been reported following re-exposure to Synagis (palivizumab) [see Adverse Reactions, Post-Market-

Continued on next page

ing Experience]. Rare severe acute hypersensitivity reactions have also been reported on initial exposure or re-exposure to palivizumab. If a severe hypersensitivity reaction occurs, therapy with palivizumab should be permanently discontinued. If milder hypersensitivity reactions occur, caution should be used on readministration of palivizumab. If anaphylaxis or severe allergic reaction occur, administer appropriate medications (e.g., epinephrine) and provide supportive care as required.

PRECAUTIONS

General: Synagis® (palivizumab) is for intramuscular use only. As with any intramuscular injection, Synagis® (palivizumab) should be given with caution to patients with thrombocytopenia or any coagulation disorder.

The safety and efficacy of Synagis® (palivizumab) have not been demonstrated for treatment of established RSV disease.

The single-use vial of Synagis® (palivizumab) does not contain a preservative. Injections should be given within 6 hours after reconstitution.

Drug Interactions: No formal drug-drug interaction studies were conducted. In the IMpact-RSV trial, the proportions of patients in the placebo and Synagis® (palivizumab) groups who received routine childhood vaccines, influenza vaccine, bronchodilators or corticosteroids were similar and no incremental increase in adverse reactions was observed among patients receiving these agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis, mutagenesis and reproductive toxicity studies have not performed.

Pregnancy: Pregnancy Category C: Synagis® (palivizumab) is not indicated for adult usage and animal reproduction studies have not been conducted. It is also not known whether Synagis® (palivizumab) can cause fetal harm when administered to a pregnant woman or could affect reproductive capacity.

ADVERSE REACTIONS

In the combined pediatric prophylaxis studies of pediatric patients with BPD or prematurity involving 520 subjects receiving placebo and 1,168 subjects receiving 5 monthly doses of Synagis® (palivizumab), the proportions of subjects in the placebo and Synagis® (palivizumab) groups who experienced any adverse event or any serious adverse event were similar.

Most of the safety information was derived from the IMpact-RSV trial. In this study, Synagis® (palivizumab) was discontinued in five patients: two because of vomiting and diarrhea, one because of erythema and moderate induration at the site of the fourth injection, and two because of pre-existing medical conditions which required management (one with congenital anemia and one with pulmonary venous stenosis requiring cardiac surgery). Seizures were reported in 0.6% of the placebo group and 0.4% of the Synagis® (palivizumab) group. Deaths in study patients occurred in five of 500 placebo recipients and four of 1,002 Synagis® (palivizumab) recipients. Sudden infant death syndrome was responsible for two of these deaths in the placebo group and one death in the Synagis® (palivizumab) group. Adverse events which occurred in more than 1% of patients receiving Synagis® (palivizumab) in the IMpact-RSV study for which the incidence in the Synagis® (palivizumab) group was 1% greater than in the placebo group are shown in Table 1.

Table 1. Adverse Events Occurring in IMpact-RSV Study at Greater Frequency in the Synagis® (palivizumab) Group

% of patients with:	Placebo n = 500	Synagis® (palivizumab) n = 1,002
upper respiratory infection	49.0%	52.6%
otitis media	40.0%	41.9%
rhinitis	23.4%	28.7%
rash	22.4%	25.6%
pain	6.8%	8.5%
hernia	5.0%	6.3%
SGOT increased	3.8%	4.9%
pharyngitis	1.4%	2.6%

Other adverse events reported in more than 1% of the Synagis® (palivizumab) group included: fever, cough, wheeze, bronchiolitis, pneumonia, bronchitis, asthma, croup, dyspnea, sinusitis, apnea, failure to thrive, nervousness, diarrhea, vomiting, and gastroenteritis, SGPT increase, liver function abnormality, study drug injections site reaction, conjunctivitis, viral infection, oral monilia, fungal dermatitis, eczema, seborrhea, anemia and flu syndrome. The incidence of these adverse events was similar between the Synagis® (palivizumab) and placebo groups.

IMMUNOGENICITY: In the IMpact-RSV trial, the incidence of anti-palivizumab antibody following the fourth injection was 1.1% in the placebo group and 0.7% in the Synagis® (palivizumab) group. In pediatric patients receiving Synagis® (palivizumab) for a second season, one-six patients had transient, low titer reactivity. This reactivity was not associated with adverse events or alterations in Synagis® (palivizumab) serum concentrations.

These data reflect the percentage of patients whose test results were considered positive for antibodies to Synagis® (palivizumab) in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Synagis® (palivizumab) with the incidence of antibodies to other products may be misleading.

POST-MARKETING EXPERIENCE:

The following adverse reactions have been identified and reported during post-approval use of Synagis® (palivizumab). Because the reports of these reactions are voluntary and the population is of uncertain size, it is not always possible to reliably estimate the frequency of the reaction or establish a causal relationship to drug exposure.

Based on experience in over 400,000 patients who have received Synagis® (palivizumab) (>2 million doses), rare severe acute hypersensitivity reactions have been reported on initial or subsequent exposure. Very rare cases of anaphylaxis (<1 case per 100,000 patients) have also been reported following re-exposure. None of the reported hypersensitivity reactions were fatal. Hypersensitivity reactions may include dyspnea, cyanosis, respiratory failure, urticaria, pruritis, angioedema, hypotonia and unresponsiveness. The relationship between these reactions and the development of antibodies to Synagis® (palivizumab) is unknown.

Limited information from post-marketing reports suggests that, within a single RSV season, adverse events after a sixth or greater dose of Synagis® (palivizumab) are similar in character and frequency to those after the initial five doses.

OVERDOSAGE

No data from clinical studies are available on overdosage. No toxicity was observed in rabbits administered a single intramuscular or subcutaneous injection of Synagis® (palivizumab) at a dose of 50 mg/kg.

DOSAGE AND ADMINISTRATION

The recommended dose of Synagis® (palivizumab) is 15 mg/kg of body weight. Patients, including those who develop an RSV infection, should receive monthly doses throughout the RSV season. The first dose should be administered prior to commencement of the RSV season. In the northern hemisphere, the RSV season typically commences in November and lasts through April, but it may begin earlier or persist later in certain communities.

Synagis® (palivizumab) should be administered in a dose of 15 mg/kg intramuscularly using aseptic technique, preferably in the anterolateral aspect of the thigh. The gluteal muscle should not be used routinely as an injection site because of the risk of damage to the sciatic nerve. The dose per month = [patient weight (kg) × 15 mg/kg ÷ 100 mg/mL of Synagis® (palivizumab)]. Injection volumes over 1 mL should be given as a divided dose.

Preparation for Administration

- To reconstitute, remove the tab portion of the vial cap and clean the rubber stopper with 70% ethanol or equivalent.
- Both the 50 mg and 100 mg vials contain an overfill to allow the withdrawal of 50 milligrams or 100 milligrams respectively when reconstituted following the directions described below.
- Slowly add 0.6 mL of sterile water for injection to the 50 mg vial or add 1.0 mL of sterile water for injection to the 100 mg vial. The vial should be gently swirled for 30 seconds to avoid foaming. DO NOT SHAKE VIAL.
- Reconstituted Synagis® (palivizumab) should stand at room temperature for a minimum of 20 minutes until the solution clarifies.
- Reconstituted Synagis® (palivizumab) does not contain a preservative and should be administered within 6 hours of reconstitution.

To prevent the transmission of hepatitis viruses or other infectious agents from one person to another, sterile disposable syringes and needles should be used. Do not reuse syringes and needles.

HOW SUPPLIED

Synagis® (palivizumab) is supplied in single use vials as lyophilized powder to deliver either 50 milligrams or 100 milligrams when reconstituted with sterile water for injection.

50 mg vial NDC 60574-4112-1

Upon reconstitution the 50 mg vial contains 50 milligrams Synagis® (palivizumab) in 0.5 mL.

100 mg vial NDC 60574-4111-1

Upon reconstitution the 100 mg vial contains 100 milligrams Synagis® (palivizumab) in 1.0 mL.

Upon receipt and until reconstitution for use, Synagis® (palivizumab) should be stored between 2 and 8°C (35.6° and 46.4°F) in its original container. Do not freeze. Do not use beyond the expiration date.

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Shown in Product Identification Guide, page 324

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Ethyol® (amifostine), see Listing under MedImmune Oncology, Inc.

ETHYOL°
[a-thi-ol]
AMIFOSTINE for Injection
IV only

DESCRIPTION

ETHYOL° (amifostine) is an organic thiophosphate cytective agent known chemically as 2-[(3-aminopropyl no]ethanethiol dihydrogen phosphate (ester) and following structural formula:

$$H_2N(CH_2)_3NH(CH_2)_2S\text{-}PO_3H_2$$

Amifostine is a white crystalline powder which is freely uble in water. Its empirical formula is $C_5H_{15}N_2O_3PS$ has a molecular weight of 214.22.

ETHYOL° is the trihydrate form of amifostine and is plied as a sterile lyophilized powder requiring reconstion for intravenous infusion. Each single-use 10 mL contains 500 mg of amifostine on the anhydrous b

CLINICAL PHARMACOLOGY

ETHYOL° is a prodrug that is dephosphorylated by line phosphatase in tissues to a pharmacologically free thiol metabolite. This metabolite is believed sponsible for the reduction of the cumulative renal of cisplatin and for the reduction of the toxic effects ation on normal oral tissues. The ability of **ETHYOL°** ferentially protect normal tissues is attributed to the capillary alkaline phosphatase activity, higher pH ter vascularity of normal tissues relative to tumors which results in a more rapid generation of the active metabolite as well as a higher rate constant for uptake cells. The higher concentration of the thiol metabolite normal tissues is available to bind to, and thereby reactive metabolites of cisplatin. This thiol metabolite also scavenge reactive oxygen species generated by exposure to either cisplatin or radiation.

Pharmacokinetics: Clinical pharmacokinetic studies that **ETHYOL°** is rapidly cleared from the plasma distribution half-life of <1 minute and an elimination